

TOBI® Podhaler™
(Tobramycin Inhalation Powder 28 mg capsules)
For the management of cystic fibrosis patients with
Pseudomonas aeruginosa

FDA Anti-Infective Drugs Advisory Committee Meeting
Briefing Document
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Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Introduction

The ion transport defects in cystic fibrosis (CF) lead to low volumes of fluids essential to the function of mucosal surfaces and secretory organs. In the lung, the small volumes of thick viscid mucus predispose to chronic infections with *Pseudomonas aeruginosa*. The applicant of this New Drug Application (NDA) presents two placebo controlled trials and one comparative safety trial to provide evidence of the safety and efficacy of TOBI Podhaler (referred to as TIP in the rest of this document), a powder formulation of tobramycin for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. The active ingredient, tobramycin, is identical to the active ingredient in the intravenous formulation of tobramycin (approved since 1976 for the treatment of *Pseudomonas aeruginosa* in patients with CF) and the inhaled tobramycin solution TOBI® (approved since 1997 for the same indication). TIP is a dry powder packaged in a hard capsule. Drug delivery for this new powder formulation of tobramycin is via a handheld, manually operated, breath-activated T-326 dry powder inhaler. The T-326 dry powder inhaler, intended for replacement every 7 days, is not an FDA-cleared device. TIP is to be administered as four capsules equaling 112 mg of tobramycin twice daily for repeated cycles of 28 days on drug and 28 days off drug.

Treatment of *P. aeruginosa* in Cystic Fibrosis

The Cystic Fibrosis Foundation (CFF) guidelines recommend that CF patients have at least 4 respiratory cultures per year. When *P. aeruginosa* is detected in a respiratory culture for the first time, eradication is usually attempted. Although eradication may be achieved initially, in most cases, patients will eventually develop chronic *P. aeruginosa* colonization. CFF guidelines strongly recommend chronic use of inhaled tobramycin in CF patients 6 years and older with FEV1% predicted <40 to 69¹ and persistent *P. aeruginosa* in airway cultures. The CFF also recommends inhaled tobramycin use in asymptomatic CF patients 6 year older; however, the evidence supporting this recommendation is weaker. The duration of ‘chronic’ therapy is not defined. In clinical practice, patients generally remain on cycled inhaled antibacterial drugs indefinitely.

Indication and Treatment Alternatives

The proposed indication for TIP is for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*.

There are two approved products for the management of *Pseudomonas aeruginosa* in patients with CF; the approved indication varies for these two products although their clinical use is similar. Both are inhaled liquid formulations administered by inhalation with nebulizers. TOBI® is a tobramycin solution formulated for inhalation via a nebulizer and compressor. It is specifically indicated for use with the Pari LC Plus nebulizer and Pulmo-aide air compressor. The treatment dose is 300 mg inhaled delivered twice daily. TOBI® is taken for repeated cycles of 28 days on drug and 28 days off drug. Cayston® is aztreonam

¹ Flume PA, O’Sullivan BP, Robinson KA, et al Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health Am J Respir Crit Care Med 176:957-969, 2007

formulated for inhalation via the Altera nebulizer (75mg TID). It is indicated to improve respiratory symptoms in CF patients with *P. aeruginosa*. However, it is FDA approved for 28 days of therapy and not approved for chronic cycled therapy. In the clinical setting, it is often used in a manner similar to TOBI®.

Overview of Drug Development

This briefing package presents the FDA analysis of the information supporting this new drug application and is intended to augment the information contained in the applicant's briefing package.

The key clinical trials and their role in the drug development for TIP are:

1. INH 007 – to assess the suitability of the TIP T-326 Inhaler drug-device combination for the inhaled administration of tobramycin
2. TPI 001- dose-ranging study to identify a TIP dose that achieves comparable tobramycin serum and lung exposures of to those achieved with TOBI®
3. C2301 and C2303 – to demonstrate superior efficacy of TIP to placebo in FEV1, (primary) microbiological activity, and clinical outcomes
4. C2302 - to demonstrate clinical comparability of inhaled tobramycin dry powder (TIP) to nebulized tobramycin solution (TOBI®) with respect to safety, microbiological activity, pharmacokinetics, clinical outcomes (lung function, Cystic Fibrosis Questionnaire - Revised [CFQ-R]) administration time, Treatment Satisfaction Questionnaire for Medication [TSQM] EuroQol Questionnaire [EQ-5D])

Details on the population characteristics and study execution are shown in TABLE 1.

TABLE 1
Key trials supporting the New Drug Application for TOBI Podhaler (TIP)

Trial (Phase) Objectives Design	Population characteristics	Drug Exposure	Study Populations (n)	Formulation
INH -007 (Phase 1) Deposition, PK, Open Label, TIP vs TOBI®	Normal adult volunteers Mean age 34 years With FEV1 >80%	2-part 5 period crossover TIP vs TOBI®	Planned 16 Enrolled (Safety) 14 Completed 12	TS-001
TP1-001 (Phase 1) Dose Finding Open label, active controlled TIP vs TOBI®	CF patients 6 years or older with FEV1>40% predicted	Single dose TOBI® vs single dose TIP 2x 14 mg 4 x 14 mg 2 x 28 mg 3 x 28 mg	Planned 80 Randomized 90 TOBI® 20 TIP 66 28 mg 11 56 mg 13 56 mg 14 84 mg 15	TS-001

NDA-201688 TOBI/PODHALER (Tobramycin Inhalation Powder 28 mg capsules)
For the management of cystic fibrosis patients with *Pseudomonas aeruginosa*

		4 x 28 mg	112 mg 13	
C2301 (Phase 3) Stopped early Double blind TIP vs excipient placebo	CF patients 4 months off anti -pseudomonal antibacterial drugs Mean age 13+4.25 y.o. Race 80% Caucasian Severity 63% FEV ¹ >50 Sex 58% Female	Cycle 1 blinded placebo controlled Cycles 2,3 open label TIP only (4 x 28 mg BID)	Planned 140 Randomized 102 Safety 95 Completed 79 S-ITT 61 TIP 29 Placebo 32	CN1-002 original manufacturing process
C2303 (Phase 3) Failed enrollment Double blind TIP vs excipient placebo	CF patients 4 months off anti Pseudomonal antibacterial drugs Mean age 13+4.25 y.o. Race 97%Caucasian Severity 69% FEV ¹ >50 Sex 72% Female	Cycle 1, blinded, placebo controlled (4 x 28 mg BID of the to be marketed formulation)	Planned 100 Enrolled 103 Randomized 62 ITT(safety) 62 TIP* 30/32 Placebo 32/30	CN1-002 new manufacturing process
C2302 (Phase 3) Completed Active controlled TIP vs Tobramycin solution (TOBI®)	CF patients 1 month off anti Pseudomonal antibacterial drugs Age 6-74 (26 + 11.4) y.o. Race 91%Caucasian Severity 59% FEV ¹ >50 Sex 45% Female	Cycles 1-3 open label, comparative TIP (4 x 28 mg BID) vs TOBI®	Planned 500 Randomized 553 ITT 517	CN1-002 original manufacturing process

*Safety/Efficacy

Additional studies were conducted to evaluate TIP delivery via the device T-326 (TSB-001) and device usability. These studies are also discussed in this briefing document.

Chemistry

Drug product

Two formulations were used in the course of clinical development. The first formulation TS-001 was used in early clinical development whereas CN1-002 was used in later phase 2 and phase 3 studies (C2301 and C2302). The manufacturing process for CN1-002 was further modified to reduce variability in powder characteristics (C2303). The to-be-marketed drug product (TBM100, 28 mg inhalation powder hard capsule) is a white powder filled into size #2 clear, hypromellose capsules, packaged in a blister card of eight (8) TOBI Podhaler capsules (four capsules for inhalation in the morning and four capsules for inhalation in the evening). A weekly pack contains one Podhaler inhaler and its storage case and seven blister cards (one card for each day of the week); there are four weekly packs in a TOBI Podhaler package. The FDA concludes that the serum pharmacokinetics of tobramycin was not altered due to the change in manufacturing process. The data supporting this conclusion is described in the Clinical Pharmacology section of this briefing document below.

Device

The dry powder inhaler device, T-326, is a hand held, breath-actuated oral inhaler uses no power source and has a flow resistance of approximately 0.09 cm H₂O^{0.5}/LPM or about 8 cm H₂O at 30 LPM. To administer TIP, the patient must remove the mouthpiece of the T-326, load a single TIP capsule into the inhaler chamber, screw the mouthpiece back on, pierce the capsule by pressing down on the blue button, and then inhale twice. These steps must be repeated an additional 3 times to administer a full dose (4 TIP capsules=112 mg). An inhaler is provided with each weekly pack.

Study TSB 001

In the development of the T-326 device, the applicant conducted a study in CF patients in order to determine the ability (or limitations) of CF patients to receive the proper dose of a dry powder using a simulated inhaler. Study TSB-001 was designed to characterize the inspiratory flow profiles of CF patients aged 6 to 53 years, (mean age 20 years, 20% of whom had FEV₁ < 40% of predicted), measure inspiratory volumes, flows and times, and design a breath simulator to derive optimal flow characteristics and performance limitations in smaller and/or subjects with more restrictive lung disease.

Twenty-seven percent of patients were capable of inspiratory volumes of 2 liters; however, all patients achieved a peak flow rate of 30 LPM, the minimum peak flow rate required to utilize the device. It should be noted that the lowest values for peak flow rates approaching this limit were in the lowest age range and none of the patients aged 6-10 years tested had an FEV₁ <60%. Thus, Study TSB 001 did not include pediatric CF patients with the full range of inspiratory flow profiles.

Study 00-IN-007

To assess the suitability of the device T-326 in the delivery of TIP, radiolabeled TIP was compared with the approved TOBI® solution formulation in terms of the achieved lung distribution, pharmacokinetics and safety. This active-controlled study assessed dose comparison of TIP and comparison of TIP to TOBI®. In Part A (characterizing lung deposition), subjects received one inhalation of TIP, whereas in Part B (characterizing PK) subjects received 6 inhalations of TIP. These measures were compared to the approved formulation of TOBI®, administered by nebulization for 15 minutes.

The distribution of the drug in the various lung areas between a single inhalation of TIP (13 mg) and a full dose of TOBI® (300 mg) are summarized in TABLE 2. Greater distribution of tobramycin (measured as % radioactivity) was seen in the lung and mouth with TIP compared to TOBI®.

TABLE 2

Radiolabel distribution results Study 00-IN-007 (submitted by the applicant to NDA 201,688)

Table 11.3.2:1 Radiolabel distribution after inhalation of ^{99m}Tc-PulmoSphere tobramycin from the T-326 DPI and nebulization of ^{99m}Tc-TOBI

Treatment (N)	PulmoSphere Tobramycin† (13)		TOBI (13)	
	% total radioactivity	Tobramycin equivalents (mg)*	% total radioactivity	Tobramycin equivalents (mg)**
Central lung	9.3 ± 3.0	1.2 ± 0.4	1.4 ± 0.8	4.3 ± 2.3
Intermediate lung	11.3 ± 2.2	1.5 ± 0.3	1.6 ± 0.7	4.9 ± 2.1
Peripheral lung	13.7 ± 2.5	1.8 ± 0.3	1.9 ± 0.7	5.8 ± 2.1
Whole lung dose	34.3 ± 5.8	4.6 ± 0.8	5.0 ± 2.0	14.9 ± 6.2
Oropharynx, esophagus and stomach	43.7 ± 8.4	5.8 ± 1.1	8.2 ± 3.6	24.6 ± 10.9
Total body dose	78.1 ± 7.9	10.4 ± 1.1	13.2 ± 4.6	39.5 ± 13.9
Exhalation filter	0.2 ± 0.1	0.03 ± 0.02	26.2 ± 3.1‡	78.6 ± 9.3‡
T-326 inhaler	8.3 ± 2.9	1.1 ± 0.4	NA	NA
T-326 capsule	13.4 ± 6.2	1.8 ± 0.8	NA	NA
Nebulizer cup	NA	NA	55.7 ± 5.6	167 ± 16.7
Nebulizer mouthpiece and T-piece	NA	NA	4.9 ± 2.2	14.7 ± 6.5
Total not in body	21.9 ± 7.9	2.9 ± 1.1	86.8 ± 4.6	261 ± 14
Total labeled dose accounted for	100	13.3	100	300

* Based on a single inhalation of 25 mg PulmoSphere powder containing 13.27 mg of tobramycin free base

** Based on 15-minute nebulization period using a nebulizer charge of 300 mg tobramycin free base

† Mean data from Periods 1, 2, and 3.

‡ Includes activity deposited on filter during continuous nebulization.

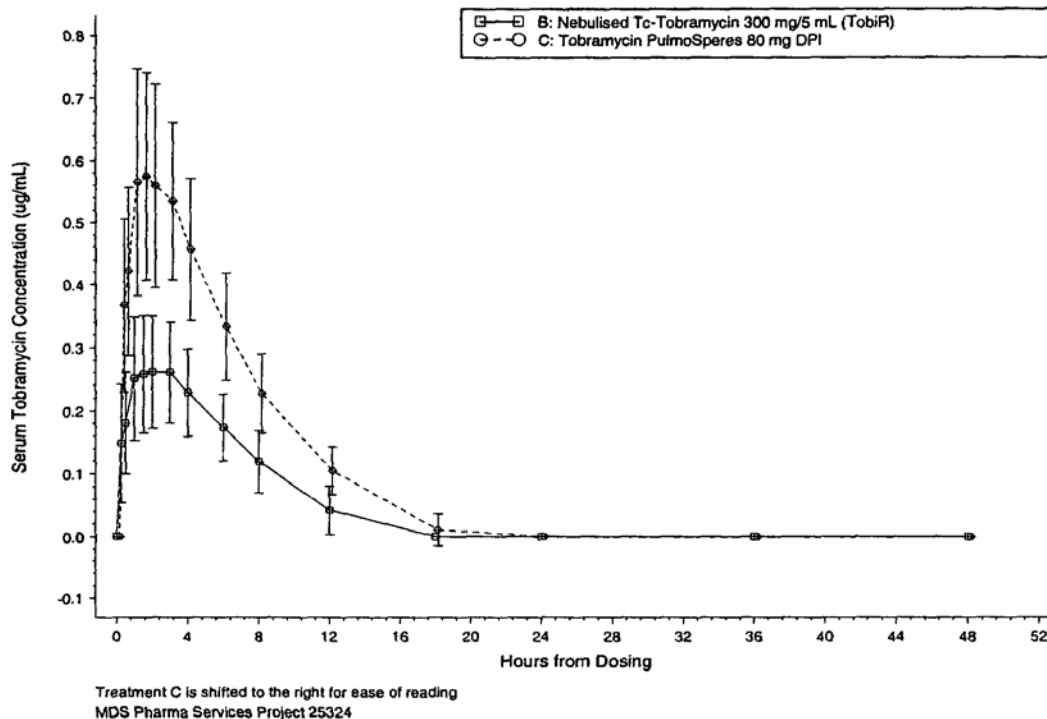
NA Not applicable

The PK comparisons in this study reflect 6 inhalations of TIP (8 inhalations of 2 per capsule constitutes a full TIP dose) compared to a full dose of TOBI®. The mean serum tobramycin concentrations achieved with a less than full dose TIP were greater compared to those achieved with full dose TOBI®, although the levels achieved were still small compared to IV delivery.

FIGURE 1

Serum tobramycin concentrations versus time Study 00-IN-007 (submitted by the applicant to NDA 201,688)

Figure 11.3.3.2:1 Mean (S.D.) Serum Tobramycin Concentrations Versus Time



Study TPI001, evaluating sputum drug concentrations, is described in the Clinical Pharmacology and Clinical Safety Sections of this briefing document.

Toxicology

TIP was well tolerated in rats given daily estimated inhaled free tobramycin doses of up to approximately 38 mg/kg for 6 months and in dogs given estimated daily inhaled free tobramycin doses of up to approximately 28 mg/kg for 28 days. The estimated pulmonary deposited free tobramycin doses for these animals were 3.8 mg/kg for rats and 5.6 mg/kg for dogs. There were no clinical signs of tobramycin toxicity in either species.

In the rats, findings such as minimal squamous hyperplasia in the larynx (often seen with inhalation of particulates), accumulation of alveolar macrophages containing pigment/basophilic debris, hyperplasia at the broncho-alveolar junction, signs of nasal inflammation, degeneration of olfactory epithelium, and minimal respiratory metaplasia of the olfactory mucosa were seen in the respiratory system. Kidney changes identical to those observed in older rats as age-related nephropathy were observed at a greater

incidence in TIP-treated rats than controls. These histopathologic findings in the respiratory tissues and kidneys of the rats are similar to those observed following chronic treatment with TOBI® solution given by nebulization.

TIP-related findings in dogs included minimal to moderate inflammation in the mucosa of the nasal turbinates (reversible) and minimal tubular degeneration/ regeneration with associated inflammation in the kidneys. Comparative toxicity of TIP to TOBI® solution was not studied in dogs.

Toxicokinetic data from both species showed that after repeated dosing with TIP, the half-life of tobramycin in serum was relatively brief (usually 1-2 hours, but up to 4.4 hours observed); however, it had a long residence time in the lungs (still quantifiable 28 days after the final dose was administered). At the highest dose in rats, C_{max} was generally 30-40 µg/ml with the AUC_{0-24 hr} approximately 100 mcg·hr/ml. At the highest dose in dogs, C_{max} was generally 3-7 mcg/ml with AUC_{0-24 hr} around 13-22 mcg·hr/ml.

The data from these studies suggest that repeated dosing with TIP would not be expected to cause greater systemic or pulmonary toxicity related to tobramycin than the currently marketed drug TOBI®.

Clinical Pharmacology

The pharmacokinetics of intravenous tobramycin are well-characterized. Tobramycin Solution for inhalation, USP (TOBI®) for the treatment of *Pseudomonas* infections in patients with cystic fibrosis is minimally absorbed from the lungs. Tobramycin is primarily excreted renally through glomerular filtration and has a serum half-life of approximately 2 hours. Serum protein binding of tobramycin is negligible, and tobramycin is not thought to undergo hepatic metabolism. Tobramycin has no appreciable oral bioavailability.

Clinical Dose Selection

The applicant conducted a single-ascending dose study (TPI001) to determine a dose of tobramycin powder (TIP) that would achieve similar serum and sputum exposures to that observed following the administration of tobramycin saline solution (TOBI® 300 mg). The serum (TABLE 3) and sputum (TABLE 4) pharmacokinetics of the approved dose of tobramycin solution TOBI® (300 mg) versus several doses of tobramycin powder for inhalation TIP are shown. FDA finds that the range of tobramycin concentrations following the administration of 112 mg of TIP is either comparable to or higher than the range of tobramycin concentrations throughout the 12 hour time course, following the administration of 300 mg TOBI. Based on the results of TIP001, the Applicant selected TIP 4x28 mg (total TIP dose of 112 mg) as a dose for further evaluation.

TABLE 3

Selected Pharmacokinetic Parameters of Tobramycin in Serum After Administration of TOBI® (300 mg) and TIP (28 mg, 56 mg, 84 mg, and 112 mg) Study TPI001 (submitted by the applicant to NDA 201,688)

Parameter	TOBI® 300 mg (n = 20)	TIP 2 × 14 mg (n = 11)	TIP 4 × 14 mg (n = 13)	TIP 2 × 28 mg (n = 13)	TIP 3 × 28 mg (n = 15)	TIP 4 × 28 mg (n = 12)
C _{max} (µg/mL)	1.04 ± 0.58	0.33 ± 0.09	0.56 ± 0.23	0.50 ± 0.21	0.70 ± 0.33	1.02 ± 0.53
T _{max} ^a (hr)	1 (0.5 – 2)	1 (0.5 – 2)	1 (0.5 – 1)	1 (0.5 – 2)	1 (1 – 2)	1 (0.5 – 2)
AUC _{inf} (µg·hr/mL)	5.3 ± 2.6	1.7 ± 0.6	3.1 ± 0.8	2.9 ± 1.2	4.1 ± 1.5	5.1 ± 2.0
AUC ₀₋₁₂ (µg·hr/mL)	4.8 ± 2.5	1.3 ± 0.6	2.8 ± 0.9	2.5 ± 1.2	3.5 ± 1.3	4.6 ± 2.0
Half-life (hr)	3.0 ± 0.8	2.8 ± 1.1	3.5 ± 0.8	3.3 ± 0.8	3.4 ± 1.0	3.1 ± 0.4

^a Presented as median (range)

TABLE 4

Selected Pharmacokinetic Parameters of Tobramycin in Sputum after Administration of TOBI® (300 mg) and TIP (28 mg, 56 mg, 84 mg, and 112 mg) Study TPI001 (submitted by the applicant to NDA 201,688)

Parameter	TOBI® 300 mg (n = 20)	TIP 2 × 14 mg (n = 11)	TIP 4 × 14 mg (n = 12)	TIP 2 × 28 mg (n = 13)	TIP 3 × 28 mg (n = 15)	TIP 4 × 28 mg (n = 11)
C _{max} (µg/mL)	737 ± 1028	258 ± 149	515 ± 421	574 ± 527	1092 ± 1052	1048 ± 1080
T _{max} ^a (hr)	0.5 (0.5 – 2)	0.5 (0.5 – 0.5)	0.5 (0.5 – 1)	0.5 (0.5 – 4)	0.5 (0.5 – 2)	0.5 (0.5 – 1)
AUC _{inf} (µg·hr/mL)	1302 ± 1127	390 ± 139	1741 ± 1173	855 ± 469	2044 ± 1334	1740 ± 809
AUC ₀₋₁₂ (µg·hr/mL)	974 ± 1143	261 ± 148	1195 ± 1224	652 ± 421	1340 ± 1320	1307 ± 978
Half-life (hr)	1.7 ± 1.6	0.9 ± 0.8	1.8 ± 0.9	1.3 ± 1.5	0.8 ± 0.8	2.2 ± 1.7

^a Presented as median (range)

Evaluation of the TIP Manufacturing Process Change on PK

The applicant altered the TIP manufacturing process prior to initiation of study C2303, thus C2303 is the only clinical study evaluating the efficacy and safety of the to-be-marketed

formulation CN1-002 manufactured under this process. To demonstrate that the pharmacokinetics of tobramycin were not altered due to the change in the manufacturing process, the applicant developed a population pharmacokinetic model for serum tobramycin based on the TIP rich pharmacokinetic data from TPI001 and sparse pharmacokinetic data from studies C2301 and C2302, conducted with the CN1-002 formulation using the initial manufacturing process for TIP. A posterior predictive check approach was used to assess whether the TIP pharmacokinetic data from the previous manufacturing process was comparable to the TIP pharmacokinetic data from the new manufacturing process. Predictions from the population pharmacokinetic model developed using data from the original manufacturing process were compared to the observed pharmacokinetic data from the new manufacturing process. Based on these results, the FDA agrees that the applicant's population pharmacokinetic model is valid, and that the serum pharmacokinetics of tobramycin were not altered due to the new manufacturing process.

Exposure-response efficacy and safety analyses

Sparse PK assessments were performed in both the TIP (n=30) and TOBI® (n=14) arms in C2302. However, due to storage beyond the validated stability window, only a subset of PK samples (TIP: n=12; TOBI®: n=6) were appropriate for inclusion in subsequent exposure-response analyses; precluding any meaningful exposure-response analyses.

Clinical Efficacy

The applicant presents data from three Phase 3 clinical trials.

Study C2301

Study Design

This was a double-blind, placebo-controlled trial over a 56 day period (1 cycle) consisting of 28 days on-therapy (TIP vs. Placebo) followed by 28 days off-therapy in CF patients ≥ 6 years of age with screening FEV1 % predicted between 25% and 80%. The initial placebo-controlled cycle was followed by an open-label extension period of 2 cycles (or 16 weeks) where all patients received 4 weeks of TIP therapy followed by 4 weeks off-TIP therapy in each cycle. This trial randomized 102 patients (48 TIP, 54 Placebo) 1:1 to receive TIP via inhalation or placebo. Patients were enrolled between September 2005 and February 2007 at 33 investigative sites in North America (n=24), Latin America (n=39), and Europe (n=39). Patients were evaluated for a total of 3 cycles (168 days or 24 weeks).

Study Conduct

This study had originally planned to enroll 140 subjects with the potential for early stopping when information from approximately 80 patients became available. Following the original interim analysis of 79 subjects in which the pre-defined stopping boundary was met for the primary endpoint ($p=.0001$, $< .0080$), the trial was stopped early by the

independent data monitoring committee overseeing the trial. A total of 18 patients were determined to have unacceptable spirometry data by the expert panel and were excluded from the interim efficacy analysis but included in safety analyses. An efficacy analysis was thus conducted based on the available data from 61 subjects (29 TIP, 32 Placebo). The pre-defined stopping boundary was also met in this population ($p=.0016 < .0044$).

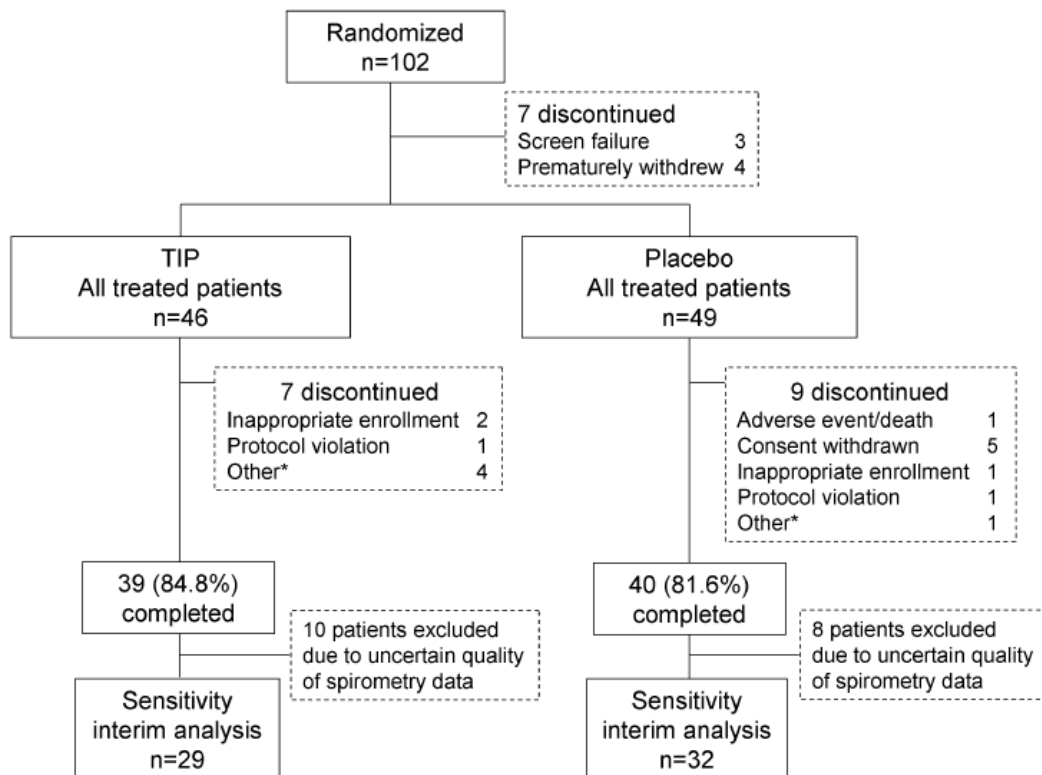
Primary Endpoint

The primary endpoint for this trial was change from baseline in the relative change in FEV1 % predicted from baseline (Day 1 of drug treatment) to the end of study drug treatment (Day 28) of the first cycle.

Primary Analysis Population

The FDA primary analysis population consisted of 61 patients (29 TIP, 32 Placebo). As described above, Study C2301 had included 95 patients in the randomized safety population who received study drug treatment. Exclusions are discussed under Study Conduct above and shown in FIGURE 2. The FDA primary analysis population is referred to in FIGURE 2 as the “sensitivity interim analysis” (SIA) population.

FIGURE 2
Study C2301 Study Population (submitted by the applicant to NDA 201,688)



*Includes moved, intolerant of inhaler, non-compliance and self discontinuation

Demographic characteristics were generally balanced across the TIP and placebo arms in both the randomized safety and the FDA primary analysis population.

TABLE 5
Study C2301 Demographic Characteristics

Variable	Randomized Safety Population (N=95)		FDA Primary Analysis Population (N=61)	
	TIP N=46	Placebo N=49	TIP N=29	Placebo N=32
Gender n (%)				
Male	19 (41.3)	23 (46.9)	13 (44.8)	18 (56.3)
Female	27 (58.7)	26 (53.1)	16 (55.2)	14 (43.8)
Severity; n(%)				
FEV1 % pred. < 50%	17 (37.0)	18 (36.7)	10 (34.5)	10 (31.3)
FEV1 % pred. ≥ 50%	29 (63.0)	31 (63.3)	19 (65.5)	22 (68.8)
Age group; n (%)				
≥ 6 yrs to < 13 yrs	21 (45.7)	24 (49.0)	11 (37.9)	13 (40.6)
≥ 13 yrs to ≤ 22 yrs	25 (54.3)	25 (51.0)	18 (62.1)	19 (59.4)
Race				
Caucasian	37 (80.4)	43 (87.8)	25 (86.2)	29 (90.6)
Other	9 (19.6)	6 (12.2)	4 (13.8)	3 (9.4)
Mean Age (years)				
Mean ± SD (Median)	13.4±4.42 (14.0)	13.2±3.91 (13.0)	13.8 ± 3.82 (14.0)	14.1± 4.16 (14.5)
Region				
North America	11 (23.9)	12 (24.5)	9 (31.0)	11 (34.4)
Latin America	17 (37.0)	17 (34.7)	3 (10.3)	5 (15.6)
Europe	18 (39.1)	20 (40.8)	17 (58.6)	16 (50.0)

FDA Primary Analysis Methodology

The applicant's primary analysis included only those patients in the sensitivity interim analysis (SIA) with observed changes from baseline in FEV1 % predicted at Day 29; thus there were 3 patients (2 TIP, 1 Placebo) with missing values for the relative change in FEV1 % predicted at Day 28 who were excluded from the applicant's primary analysis. The FDA statistical reviewer's primary analysis included all 61 SIA patients. For the 3 patients (2 TIP, 1 Placebo) with missing values for the relative change in FEV1 % predicted at Day 28 who were excluded from the applicant's primary analysis, a value of -0.57% was imputed. Under the FDA statistical reviewer's imputation scheme, a value of -0.57% corresponds to the minimum of 0 and the least favorable treatment mean among the 59 patients with observed values at Day 28 (i.e. -0.57% in the placebo arm). This imputation scheme assumes that patients with missing FEV1 % predicted measurements at a given visit would not have a relative change greater than '0' (i.e. no improvement from baseline) and would also not have a relative change that is favorable to the other group mean (i.e. no treatment benefit).

The FDA statistical reviewer's primary analysis also considered a non-parametric test (i.e. test based on the rank of the relative changes in FEV1 % predicted rather than the actual values) using an ANCOVA model with factors for treatment, age, region and baseline FEV1 % predicted. Non-parametric analyses were used because the distribution of relative

changes in FEV1% predicted was not observed to follow a normal distribution. For example, the distribution of TIP patients was observed to be highly, positively skewed. In addition, the FDA statistical reviewer's primary analysis included a sensitivity analysis which considered all randomized and treated patients (N=95) in order to account for biases which may result from the exclusion of 34 potentially informative patients (17 in each arm) who received treatment therapy. In this sensitivity analysis, missing values were imputed using the placebo group mean of -0.57% (i.e. the minimum of 0 and the least favorable group mean) as performed in the Reviewer's primary analysis and other Reviewer analyses.

Primary Analysis Results

The applicant's primary analysis (i.e. parametric ANCOVA) and FDA's primary analysis (i.e. non-parametric ANCOVA) are compared in TABLE 6. Additional parametric and non-parametric analyses (i.e. t-test, Wilcoxon Rank Sum test, FDA's parametric ANCOVA) are also compared. The FDA primary analysis showed significantly higher relative improvements from baseline in FEV1 % predicted at Day 28. Non-parametric analyses showed more conservative results compared to parametric analyses.

TABLE 6

Applicant and FDA Analysis of Primary Endpoint: Relative Change from Baseline in FEV1 % Predicted at Day 28 (Study C2301 SIA Population)

	TIP (N=29)	Placebo (N=32)	Mean Treatment Difference (SE)	95% CI for Difference	P-value
Applicant Analysis					
Adjusted Mean (%)	13.97	0.68	13.29 (3.98)	(5.31, 21.28)	p=.0016 ¹
Unadjusted Mean (%)	13.21	-0.57	13.79 (3.95)	(5.87, 21.70)	p=.0010
FDA Analysis					
Adjusted Mean (%)	12.54	0.09	12.44 (3.77)	(4.89, 20.00)	p=.0017 p=.0061 ²
Unadjusted Mean (Median) (%)	12.26 (9.52)	-0.57 (-0.29)	12.83 (3.80)	(5.23, 20.44)	p=.0013 p=.0070 ³

1 Applicant's primary analysis- parametric ANCOVA test adjusted for age, region and baseline FEV1 % predicted, using observed data in 58 patients (27 TIP, 31 Placebo)

2 FDA's primary analysis- non-parametric ANCOVA based on ranks adjusted for age, region and baseline FEV1 % predicted, using imputed data

3 FDA's sensitivity analysis- Unadjusted non-parametric test (Wilcoxon Rank Sum test) using imputed data

The FDA statistical reviewer's sensitivity analysis using all randomized (treated) patients also showed findings to be significant at the $\alpha=.05$ level but only marginally so based on the Wilcoxon rank sum test (p=0.035). Adjusted estimates for the mean treatment difference were approximately 8.14% in the all randomized (treated) analysis, substantially below what was observed in the FDA primary analysis population (i.e. 12.44%) in Table 6. Although this sensitivity analysis does not show that patient exclusions were likely to have affected the significance of findings at the $\alpha=.05$ level, it does suggest a high degree of

uncertainty in assessing the strength of significant findings below the $\alpha=.05$ level. It should be noted that an additional 7 subjects (2 TIP, 5 Placebo) who were randomized but never treated were excluded from this analysis. However, the impact of these 7 subjects on observed p-values was found to be negligible.

TABLE 7

FDA Reviewer's Sensitivity Analysis of the Primary Endpoint: Relative Change from Baseline in FEV1 % Predicted at Day 28 Using Imputed Data⁵ (C2301 All Randomized Safety)

	TIP N=46	Placebo N=49	Mean Treatment Difference (SE⁴)	95% CI for Mean Difference	P-value
Adjusted Mean	6.88	-1.26	8.14 (3.07)	(2.05, 14.23)	p=.009 ¹ p=.023 ²
Unadjusted Mean	7.52	-0.57	8.09 (3.08)	(1.97, 14.21)	p=.010 p=.035 ³

1 Parametric ANCOVA adjusted for covariates of age and region

2 Non-parametric ANCOVA based on ranks adjusted for covariates of age and region

3 Non-parametric Wilcoxon Rank Sum test

4 Variance estimates in parametric tests are based on only those patients with observed relative change values

5 Missing data for 37 subjects (19 TIP, 18 Placebo) who received study drug were imputed.

Source: Reviewer Table

Distribution of Relative Changes in FEV1 % Predicted

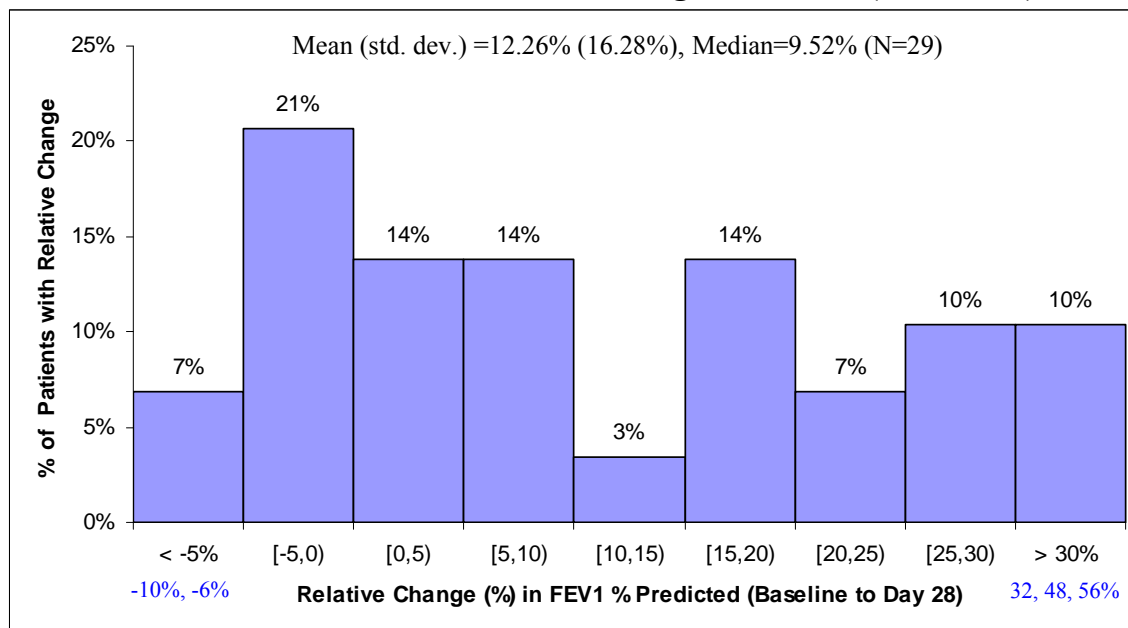
FIGURES 3 & 4 show the distribution of the primary endpoint, relative changes in FEV1 % predicted from baseline to Day 28, in each of the treatment arms for Study C2301 (SIA-ITT population), as evaluated in the reviewer's primary analysis. TIP relative changes appeared to be highly skewed in the positive direction with a mean of 12.26% vs. a median of 9.52%. This positive tendency was primarily observed in patients under the age of 13 years and patients with FEV1 $\geq 50\%$ predicted, where the mean relative changes greatly exceeded median relative changes. In contrast to the TIP distribution, relative changes in the placebo arm had a similar mean and median of -0.57% and -0.29%, respectively. The placebo distribution, however, did exhibit relative "heaviness" near the outer regions of the distribution (e.g. for relative changes of approximately $\pm 20\%$ or 1.5 standard deviations from the mean).

When comparing the distributions of relative changes between the treatment arms, the most pronounced differences favoring TIP over placebo were in patients with more extreme relative changes (i.e. relative changes in the tails of the distributions), especially the right (positive) tail. In the right tail, the most favorable (next most favorable) relative change among TIP patients of 56% (48%) exceeded the most favorable (next most favorable) relative change in the Placebo arm of 25% (24%) with a treatment difference of 31% (24%). In the left tail, treatment differences of 18% (18%) for the least favorable (next least favorable) relative change were not as pronounced as in the right tail but were still relatively large compared to treatment differences in the middle of the distribution which fell below 10% (e.g. TIP median = 9.5%, Placebo median = -0.3%). Based on the distributions, TIP therapy appears to provide a relatively strong benefit over placebo in a

small subgroup of patients and more modest benefit in the remaining group of patients. As stated above, reviewer analyses considered non-parametric testing for the primary analysis to control against the influence of a skewed distribution with extreme responses.

FIGURE 3

Distribution of FEV1 % Predicted Relative Changes: TIP Arm (C2301 SIA)

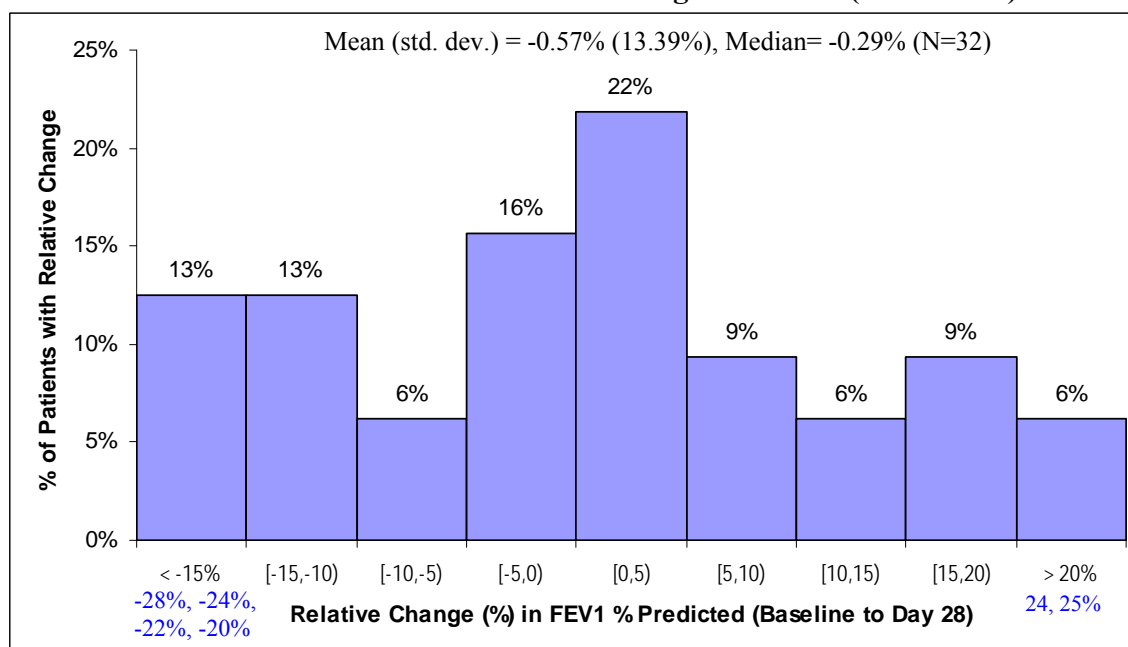


Individual patient changes (%) in FEV1 % Pred. falling in tail regions (< -5%, >30%) are shown in blue.

Source: Reviewer Figure

FIGURE 4

Distribution of FEV1 % Predicted Relative Changes: Placebo (C2301 SIA)



Individual patient changes (%) in FEV1 % pred. falling in tail regions (< -15%, > 20%) are shown in blue.

Source: Reviewer Figure

Sustainability of Relative Changes in FEV1 % Predicted

The placebo-controlled cycle (1 cycle or 8 weeks) of Study C2301 consisted of 4 weeks on-therapy (TIP vs. Placebo) followed by 4 weeks off-therapy. This was followed by an open-label extension period of 2 cycles (or 16 weeks) where all patients received 4 weeks of TIP therapy followed by 4 weeks off-TIP therapy per cycle. Assuming proper trial execution, this design can allow for an evaluation of the sustainability of the relative improvements from baseline in FEV1 % predicted. However, in Study C2301, such an evaluation was limited by several factors.

One factor was that comparisons of TIP improvements in FEV1 % predicted across cycles were not placebo-controlled since a concurrent placebo arm was not included in Cycles 2 & 3. Therefore, comparisons of improvements at different visits were all relative to baseline measurements within a treatment arm. These types of comparisons are limited because they can be more easily influenced by potential confounding variables specific to the cycle or time point considered. The Reviewer considered placebo-controlled comparisons as providing the most reliable evidence of sustainability of relative changes in FEV1 % predicted.

Another factor was substantially higher rates of missing data in visits after Week 5. For example, missing data in the TIP arm increased from 3.4% at Week 5 to 24.1% at Week 21. There was also trend in which rates of missing data were higher in the placebo arm in Weeks 2 and 5 and higher in the TIP arm after Week 5. Since missing data is likely to be informative (non-random), with a negative impact on relative improvements in FEV1 % predicted, analyses based on observed cases may involve strong biases favoring the time point (or treatment) with higher rates of missing data. Analyses based on imputed data can serve to reduce the influence of such biases but are also limited due to the high degree of uncertainty when rates of informative missing data are relatively high (e.g. after Week 5). As shown in FIGURES 5 & 6, relative changes were assessed on visits at Week 2 as well on visits following each 4 week period of on or off therapy over the 3 cycles.

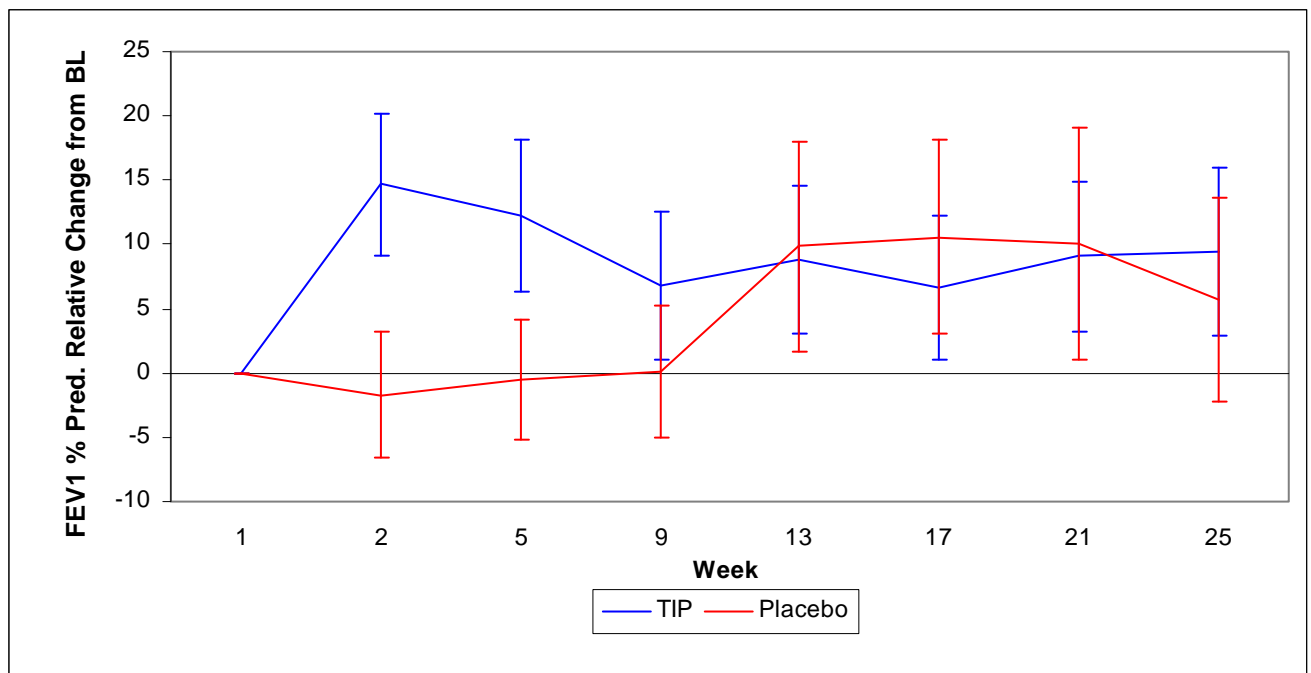
The third factor limiting an evaluation of the sustainability of relative changes in FEV1 % predicted was that relative improvements at Week 25 (i.e. the follow-up visit at the end of the study) were measured in a different manner from all other post-baseline visits. The Week 25 visit had measured FEV1 % predicted measurements 'at visit', while all other visits had taken measurements both 'pre-dose' and '30 minutes post-dose'. Applicant (and reviewer) analyses had considered relative improvements from baseline in FEV1 % predicted based on pre-dose measurements. The lack of available pre-dose measurements at Week 25 may confound comparisons of relative changes with earlier time points due to differences in study conduct.

There are also concerns regarding the reliability of the Week 25 time point vs. other time points in measuring FEV1 % predicted, based on the behavior of the observed data. Measurements taken at Week 25 often appeared to be unexpectedly extreme and inconsistent with those of other time points. For example, in TIP patients, the median

FEV1 % predicted unexpectedly increased by nearly 4% during the off-cycle between Weeks 21 to 25 (6.25% to 10.23%). This was inconsistent with that observed for patients in the placebo arm (who received TIP therapy after the first cycle) who showed a sharp decrease in the mean and median FEV1% predicted from Week 21 to Week 25. Within the placebo arm (extension period), Week 25 measurements also appeared to be inconsistent with measurements from earlier visits. Thus, the reviewer considered the time period between Week 2 and Week 21 as providing the most reliable evidence in evaluating sustainability of treatment effects. However, such a consideration greatly reduces the available information in identifying a potential trend. This is because only two (rather than three) complete cycles of TIP therapy can be compared among patients in the TIP arm and only one (rather than two) complete cycles of TIP therapy can be compared among patients in the placebo arm who received TIP during the extension period.

FIGURE 5 compares treatments at each visit based on mean relative changes from baseline in FEV1 % predicted with vertical bars representing the 95% confidence interval for the estimate. FIGURE 6 compares treatments at each visit based on median relative changes from baseline in FEV1 % predicted. In these analyses, missing values at each time point were imputed using the minimum of 0 and the least favorable group mean as performed in the reviewer's primary and other analyses.

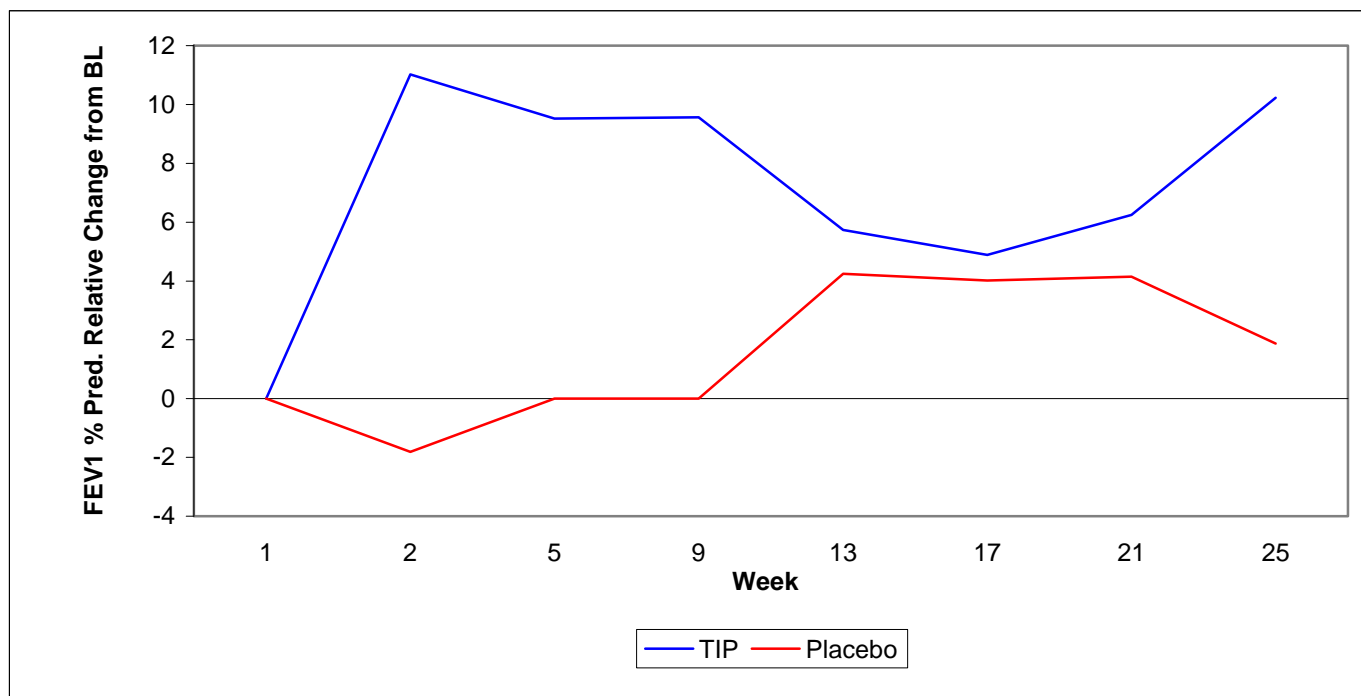
FIGURE 5
Mean FEV1 % Predicted Relative Changes Across Visits: Evaluation of the Sustainability of Effects (C2301 SIA)



Source: Reviewer Figure

FIGURE 6

Median FEV1 % Predicted Relative Changes Across Visits: Evaluation of the Sustainability of Effects (C2301 SIA-ITT)



Source: Reviewer Figure

In TABLE 8, the mean relative change from baseline in FEV1 % predicted starting Week 5 of 12.26% dropped substantially following the off-therapy period at Week 9 to 6.83% and remained at lower levels in the following cycles with mean relative changes ranging between 6.65% and 9.43%. Consistent with patients in the TIP arm who experienced a 12.26% improvement during the first on-therapy period, patients in the placebo arm experienced a 9.74% improvement following their first course of TIP therapy. Although improvements in these patients were sustained over the following 8 weeks, they had dropped substantially by the end of Cycle 3 with a mean relative change of 5.66%. Similar steep drops were observed when considering median relative changes. The median change in TIP patients of 9.52% starting Week 5 had dropped to 4.89% by the end of cycle 2 (i.e. Week 17). Placebo patients switching over to TIP therapy experienced an increase in the median relative change from 0 to 4.24% after the first course of TIP therapy at Week 13, but had a substantial drop by the end of cycle 3 (i.e. median change of only 1.87%).

TABLE 8

FDA Reviewer's Analysis of the Sustainability of Relative Changes from Baseline in FEV1 % Predicted in Subjects Using Imputed³ Data (C2301 SIA-ITT)

Visit	TIP N=29 Mean (Median)	Placebo N=32 Mean (Median)	Mean Treatment Difference (SE)	95% CI for Mean Difference	P-value
Cycle 1- TIP vs. Placebo					
Week 2	14.50 (11.02)	-1.70 (-1.81)	16.19 (3.78)	(8.63, 23.75)	p=.0001 ¹ p=.0004 ²
Week 5	12.26 (9.52)	-0.57 (-0.29)	12.83 (3.80)	(5.23, 20.44)	p=.0013 ¹ p=.0070 ²
Week 9	6.83 (9.56)	0.09 (0.00)	6.73 (3.91)	(-1.10, 14.57)	p=.0906 ¹ p=.0592 ²
Cycles 2,3- All Patients Received TIP					
Week 13	8.81 (5.74)	9.85 (4.24)	1.03 (5.17)	-	-
Week 17	6.65 (4.89)	10.58 (4.02)	-3.93 (4.84)	-	-
Week 21	9.08 (6.25)	10.09 (4.15)	-1.01 (5.60)	-	-
Week 25	9.43 (10.23)	5.66 (1.87)	3.77 (5.28)	-	-

1 Parametric t-test,

2 Wilcoxon rank sum test

Source: Reviewer Table

Subgroup Analyses

Subgroup analyses for the primary endpoint (TABLE 9 below) were explored using the same imputation scheme as in the primary analysis, in which missing values were imputed using the value of -0.57% (i.e. the minimum of 0 and the least favorable group mean among observed patients at Day 28 of -0.57%). These analyses, however, were limited by the small number of subjects included in the FDA primary analysis population (i.e. 61 subjects, 29 TIP & 32 Placebo). Relative changes from baseline in FEV1 % predicted at Day 28 were generally robust across all subgroups except for the subgroup of patients in North America, where a clear TIP benefit could not be observed. However, this analysis was limited by the small number of patients included from North America (i.e. 20 patients).

TABLE 9
Analyses of Primary Endpoint in Patients Subgroups (C2301 SIA)

Relative Change from Baseline in FEV1 % Predicted at Day 28 (Imputed Data)				
Subgroup	Subgroup Division	TIP (N=29)	Placebo (N=32)	Treatment Difference (95% CI), p-value ^{1,2}
		Mean (Median)	Mean (Median)	
Disease Severity	FEV1 < 50% pred. N=20	11.59 (12.73) n=10	-1.47 (0.67) n=10	13.06 (-1.60, 27.72), p=0.078
	FEV1 ≥ 50% pred. N=41	12.62 (7.39) n=19	-0.16 (-0.93) n=22	12.78 (3.39, 22.17), p=0.009
Region	North America N=20	1.25 (-1.90) n=9	-2.65 (-2.56) n=11	3.90 (-6.44, 14.24), p=0.438
	Latin America N=8	17.54 (-0.57) n=3	3.30 (1.90) n=5	14.24 (-30.21, 58.69), p=0.463
	Europe N=33	17.16 (19.25) n=17	-0.35 (1.19) n=16	17.51 (8.14, 26.89), p=0.006
Age Group	< 13 N=24	11.77 (7.39) n=11	-2.04 (0.77) n=13	13.81 (0.96, 26.67), p=0.036
	≥ 13 N=37	12.57 (14.50) n=18	0.44 (-0.57) n=19	12.13 (2.10, 22.15), p=0.019
Gender	Male N=31	8.23 (9.52) n=13	-2.35 (-2.21) n=18	10.57 (-0.08, 21.22), p=0.052
	Female N=30	15.54 (8.55) n=16	1.71 (1.19) n=14	13.83 (2.39, 25.28), p=0.020

¹Parametric t-test ²P-values should not be used for statistical inference due to lack of multiplicity adjustments and potential inflation of type-I error rates.

Source: Reviewer Table

Need for Anti-Pseudomonal Therapy and Other Endpoints Related to Efficacy

Supportive analyses in Study C2301 were limited by the smaller sample size than the planned 140 subjects; based on the original interim analysis in which early efficacy was observed for the primary endpoint. The study protocol was also amended such that there would be no formal testing of any secondary outcome measure (i.e. all secondary outcomes were considered to be exploratory). TABLE 10 shows findings from exploratory/other analyses using the all randomized safety population (n=95). This table shows that the proportion of patients requiring anti-pseudomonal antibacterial drugs, as determined by the FDA Clinical Reviewer, was slightly smaller in the TIP arm at 6/46 (13.0%) vs. 9/49 (18.4%) but differences were not significant, p=0.477. Trends in respiratory-related hospitalization also favored TIP patients at 4.4% vs. 12.2% but inferences were limited by the small numbers of cases (i.e. 8 cases).

TABLE 10

Other Analyses: Anti-Pseudomonal Antibacterial Drug Use and Respiratory Related Hospitalization in Cycle 1 (C2301 All Randomized Safety)

	TIP (N=46) n (%)	Placebo (N=49) n (%)	Treatment Diff. (95% CI)¹
Anti-Pseudomonal Antibacterial Drug Use	6 (13.0)	9 (18.4)	-5.3 (-20.5, 10.0), p=0.477
Respiratory Related Hospitalization	2 (4.4)	6 (12.2)	-7.9 (-4.0, 20.7), p=0.166

¹Confidence Interval Based on the Normal Approximation to the Binomial Distribution

Source: Reviewer Table

FDA Conclusions Regarding Study C2301

The Study C2301 primary analysis showed significant relative improvements in FEV1 % predicted from baseline to Day 28 in both parametric and non-parametric tests (with or without control for covariates). Findings were primarily driven by patients in Europe who experienced substantially larger relative changes compared to patients in North America.

A major limitation of Study C2301 is that the primary analysis excluded 41% of the randomized population. The analysis based on 61 (59%) of the original ITT population of 102 patients is seriously limited as the patients who dropped out could be informative. This limitation could introduce potential biases. The FDA reviewer's sensitivity analysis based on all randomized patients receiving treatment showed a smaller magnitude of treatment effect

Although both TIP and placebo patients (who crossed over) had improvements in FEV1 % predicted following their first TIP course of therapy, improvements in both of these groups diminished by the following 56 day cycle for both mean and median changes. The sustainability of improvements in FEV1 % predicted found in Study C2301 may raise concern regarding the clinical significance of these findings. In Study C2301, improvements in FEV1 % predicted were not correlated with improvements for other important clinical outcomes such as reductions in anti-pseudomonal antibacterial drug usage and reduction in respiratory hospitalizations. Supportive analyses in Study C2301 were limited as a result of using a sample size that was substantially smaller than the planned sample size of 140 subjects, and the study protocol was also amended such that there would be no formal testing of any secondary outcome measure (i.e. all secondary outcomes were considered to be exploratory).

Study C2303

Study Design

Study C2303 was a double-blind, placebo-controlled trial over a 8 week period (1 cycle) consisted of 4 weeks of on-therapy (TIP vs. placebo) followed by 4 weeks of off-therapy. Study C2303 assessed the safety and efficacy of the to-be-marketed TIP following a change in manufacturing process. The study enrolled patients between the ages of 6 and 21

diagnosed with CF due to *Pseudomonas aeruginosa* who had no exposure to inhaled anti-pseudomonal antibacterial drugs within 4 months prior to screening and had a screening FEV₁ % predicted between 25% and 80%.

Study Conduct

The trial randomized 62 patients (32 TIP, 30 Placebo) 1:1 to receive TIP (112 mg, 4x28mg capsules) or matching placebo using the T-326 dry powder inhaler. Patients were enrolled between June 2009 and May 2011 at 18 investigative sites in the following 8 countries: Bulgaria (n=12), Egypt (n=8), Estonia (n=7), India (n=1), Latvia (n=5), Lithuania (n=3), Romania (n=3) and Russia (n=23). Unlike Study C2301, Study C2303 did not include an open label extension period. Study C2303 had originally planned to enroll 100 subjects but due to challenges with enrolling TOBI® naïve patients, enrollment was terminated early.

Primary Endpoint

The primary endpoint for this trial was the relative change in FEV₁ % predicted from baseline to the end of study drug treatment (Day 29).

Primary Analysis Population

This study included 62 patients in the ITT population who received study drug treatment, 32 in the TIP arm and 30 in the placebo arm. TABLE 11 shows the baseline characteristics of patients included in the ITT population. Baseline characteristics were generally balanced across the treatment arms, however, a larger proportion of females were enrolled in TIP vs. the placebo arm (71.9% vs. 56.7%) among ITT patients.

TABLE 11
Baseline Characteristics for ITT Patients (C2303 ITT)

Variable		ITT Population (N=62)	
		TIP (N=32)	Placebo (N=30)
Gender n (%)	Male	9 (28.1)	13 (43.3)
	Female	23 (71.9)	17 (56.7)
Severity n (%)¹			
FEV ₁ % pred < 50%		10 (31.3)	9 (30.0)
FEV ₁ % pred ≥ 50%		22 (68.8)	21 (70.0)
Age group; n (%)			
≥ 6 yrs to < 13 yrs		16 (50.0)	14 (46.7)
≥ 13 yrs to ≤ 21 yrs		16 (50.0)	16 (53.3)
Race	Caucasian	31 (96.9)	30 (100)
	Other	1 (3.1)	0 (0)
Age (years)			
Mean ± SD (Median)		13.1 ± 4.25 (12.5)	12.7 ± 4.70 (14.0)

¹ Screening FEV₁ % predicted value. If missing, baseline FEV₁ % predicted value used.

Source: Reviewer Table

Primary Analysis Methodology

The applicant's pre-specified primary analysis considered relative changes in FEV1 % predicted from baseline to Day 29. This analysis excluded patients with missing FEV1 % predicted values at baseline and imputed values of '0' for patients with missing FEV1 % predicted values at Day 29. In the applicant's primary analysis, 3 patients (1 TIP, 2 placebo) with missing values for the relative change in FEV1 % predicted at Day 29 were excluded and 7 patients (6 TIP, 1 placebo) had values of '0' imputed. The applicant's primary analysis used an analysis of variance (ANOVA) model with factors of treatment, screening FEV1 % predicted (<50% and ≥50%), and age (<13 years and ≥13 years). The choice of covariates in the ANOVA was based on the randomization stratification factors.

Like the applicant's primary analysis, the FDA reviewer's primary analysis also excluded 3 patients (1 TIP, 2 placebo) with missing FEV1 % predicted values at baseline and imputed values of '0' for patients with missing FEV1 % predicted values at Day 29 (i.e. this was based on the minimum of '0' and the least favorable group mean of 2.45 in the reviewer's imputation scheme). Similarly, the reviewer's primary analysis also used an ANOVA model with factors for treatment, screening FEV1 % predicted (<50% and ≥50%), and age (<13 years and ≥13 years). However, the reviewer's primary analysis differed from the applicant's primary analysis since it considered a non-parametric test (i.e. test based on the rank of the relative changes in FEV1 % predicted rather than the actual values). Non-parametric analyses were used because the distribution of relative changes in FEV1% predicted did not follow a normal distribution. The distribution of TIP patients was observed to be highly, positively skewed.

The FDA reviewer also conducted parametric analyses for comparison with non-parametric analyses. However, the reviewer used a different approach to estimate the variance of the treatment difference. Although single imputation methods (e.g. imputing '0' for each missing value) may be adequate in providing a point estimate, they may fail to estimate the variance in an unbiased manner, especially if missing data is substantial. This is because substantial missing data will lead to imputation of a large number of '0' values which can severely bias (i.e. deflate) estimates of the variance. Under the parametric model testing assumptions, subjects are assumed to have constant variance such that the addition of new patients in the analysis would not be expected to change the variance estimate. Given these considerations, reviewer parametric analyses estimated the variance using only those patients with observed data (i.e. non-imputed data).

Primary Analysis Results

TABLE 12 shows results from both the applicant and the FDA primary analysis (i.e. parametric ANOVA) including results of the unadjusted analysis (i.e. t-test) in comparison to results from the FDA reviewer's primary analysis (i.e. non-parametric ANOVA), an unadjusted non-parametric analysis (i.e. Wilcoxon Rank Sum test), and parametric analyses (i.e. t-test and ANOVA). Regardless of the testing approach (reviewer's vs. applicant's), Study C2303 failed to show a significant improvement from baseline in FEV1 % predicted at Day 29.

TABLE 12

Applicant and FDA Analysis of the Primary Endpoint: Relative Change from Baseline in FEV1 % Predicted at Day 29 Using Imputed Data (C2303 ITT)

	TIP (N=29) N=28 ⁵	Placebo (N=32) N=30 ⁵	Mean Treatment Difference (SE ⁴)	95% CI for Mean Difference	P-value
Applicant Analysis					
Adjusted Mean	8.2	2.3	5.9 (4.03)	(-2.2, 14.0)	p=.148 ¹
Unadjusted Mean	8.3	2.4	5.8 (4.00)	(-2.2, 13.8)	p=.151
FDA Analysis					
Adjusted Mean	8.19	2.27	5.91 (4.22)	(-2.54, 14.37)	p=.167 p=.233 ²
Unadjusted Mean (Median)	8.27 (3.17)	2.45 (2.71)	5.82 (4.19)	(-2.56, 14.20)	p=.170 p=.244 ³

1 Applicant's primary analysis- parametric ANOVA adjusted for screening FEV1 % predicted (< 50% and ≥ 50%) and age (< 13 years and ≥ 13 years).

2 FDA's primary analysis- non-parametric ANOVA based on ranks adjusted for screening FEV1 % predicted (< 50% and ≥ 50%) and age (< 13 years and ≥ 13 years).

3 FDA's sensitivity analysis- Unadjusted non-parametric test (Wilcoxon Rank Sum test)

4 Variance estimates in FDA analysis included only patients with observed values.

5 Three Patients (1 TIP, 2 Placebo) with missing baseline FEV1 % predicted measurements were excluded from both the Applicant and FDA analyses.

Source: Reviewer's Table partially Adapted from Applicant Table 11-4 in the CSR

Distribution of Relative Changes in FEV1 % Predicted

FIGURES 7 & 8 show the distributions of relative changes in FEV1 % predicted from baseline to Day 29 by treatment arm in the Reviewer primary analysis. In Figure 7, TIP relative changes were highly skewed in the positive direction with a mean of 8.27% vs. a median of 2.71%. In contrast, relative changes in the Placebo arm were not directionally skewed and had a similar mean and median of 2.45% and 2.71%, respectively (Figure 8). As was observed for Study C2301, the distribution for Placebo patients in Study C2303 showed relative "heaviness" in the outer tail regions, especially in the left tail region. For example, among the 28 patients in the Placebo arm who were included in the Reviewer's primary analysis, 4 patients (14%) had large relative changes at Day 29 that were 22% (1.6 standard deviations) or more below the mean.

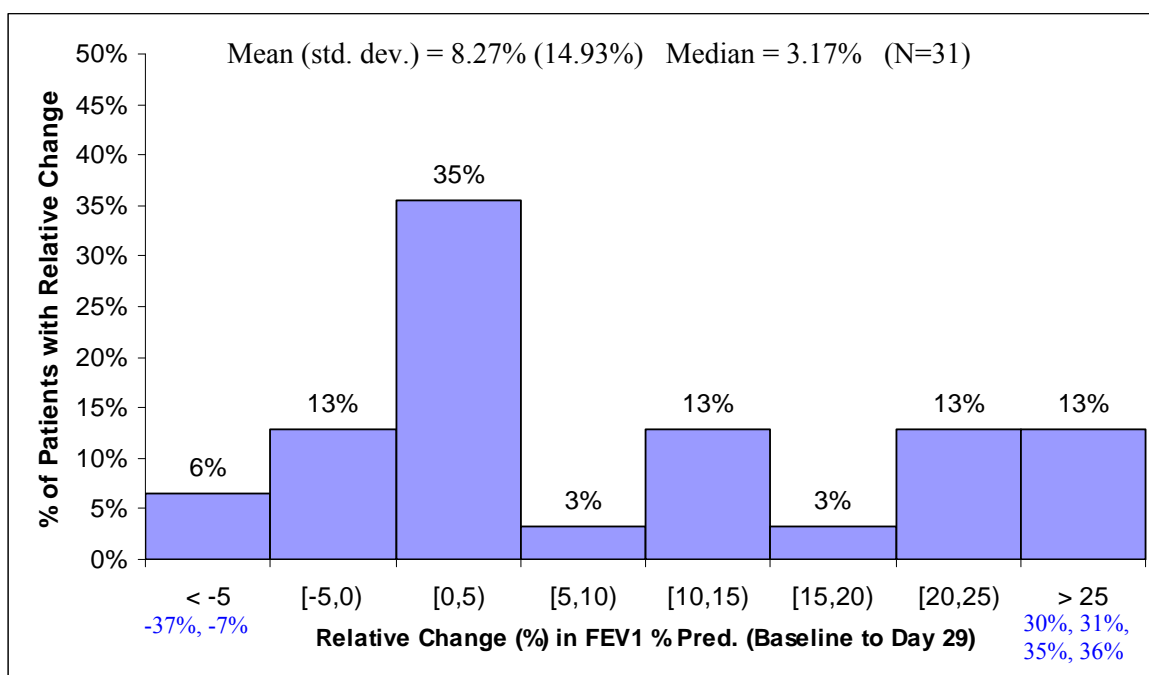
When comparing the distributions of relative changes between the treatment arms, the most pronounced differences favoring TIP over placebo were in patients with relative changes in the negative tail of the distributions. For example, aside from the outlying TIP observation of -36.7%, the next less favorable relative change in the TIP arm was only -6.9%. In the placebo arm, 7 (25%) of the patients had relative changes of -7% or worse and 4 patients (14%) had relative changes of -22.8% or worse.

Subgroup Analyses

Subgroup analyses for the primary endpoint (TABLE 13) were explored using the same imputation approach described in the primary analysis (i.e. patients with missing data at Day 29 would have a '0' imputed for their relative change value). These analyses were limited due to the small number of subjects included in the ITT primary analysis population (i.e. 62 subjects, 32 TIP & 30 placebo) from which only 59 subjects (31 TIP & 28 placebo) with available baseline FEV1 % predicted values could be included in the analyses. Relative changes from baseline in FEV1 % predicted at Day 29 were most marked in patients 13 years of age or older as well as those with FEV1 \geq 50% predicted. However, these analyses can be unduly influenced by extreme outcome measures such as a TIP patient with a -36.7% relative change who was a 7 year old male with FEV1 < 50% predicted at baseline.

FIGURE 7

Distribution of FEV1 % Pred. Relative Changes: TIP Arm (C2303 ITT)

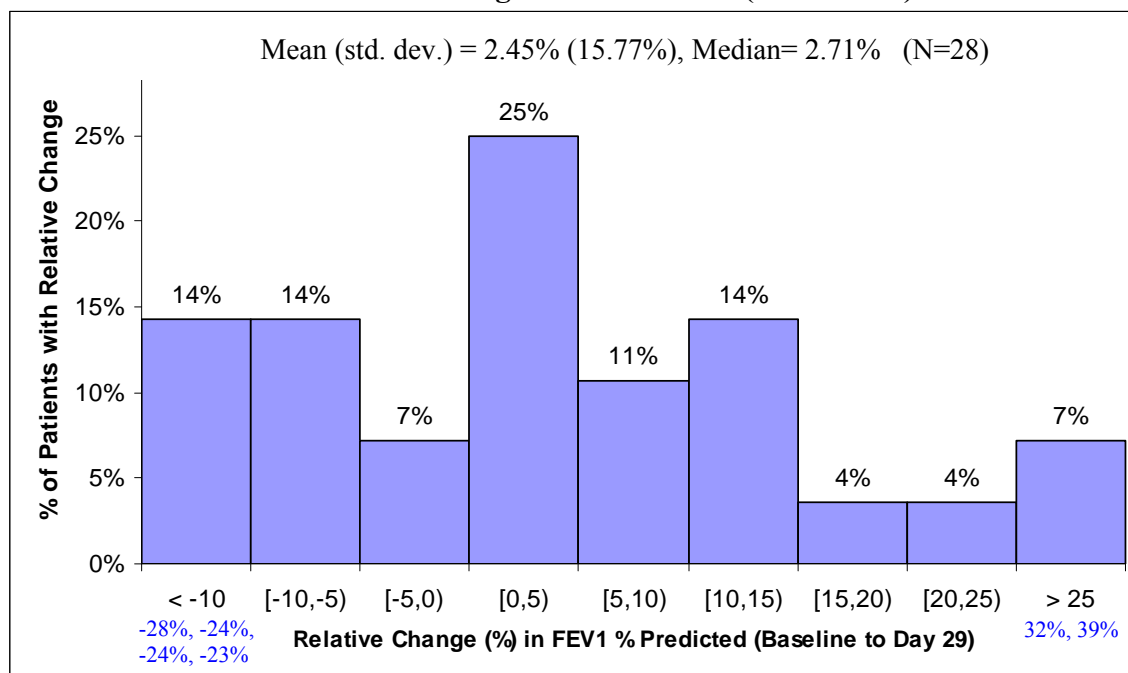


Note: Individual patients with relative changes (%) in FEV1 % predicted falling in tail regions (i.e. < -5% or > 25%) are shown in blue.

Source: Reviewer Figure

FIGURE 8

Distribution of FEV1 % Pred. Changes: Placebo Arm (C2303 ITT)



Note: Individual patients with relative changes (%) in FEV1 % predicted falling in tail regions (i.e. < -10% or > 25%) are shown in blue.

TABLE 13

Analyses of Primary Endpoint in Patients Subgroups (C2303 ITT)

Relative Change from Baseline in FEV1 % Predicted at Day 28 (Imputed Data)				
Subgroup	Subgroup Division	TIP (N=32) n=31	Placebo (N=30) n=28	Mean Treatment Difference (95% CI), p-value ^{1,2}
		Mean (Median)	Mean (Median)	
Disease Severity	FEV1 < 50% Pred. N=16	3.57 (0) n=9	8.82 (3.82) n=7	-5.25 (-27.1, 16.58), p=0.614
	FEV1 ≥ 50% Pred. N=43	10.19 (5.64) n=22	0.33 (2.56) n=21	9.87 (1.80, 17.94), p=0.018
Age Group	< 13 N=28	3.72 (1.55) n=15	2.53 (2.56) n=13	1.19 (-11.61, 13.98), p=0.850
	≥ 13 N=31	12.53 (8.18) n=16	2.37 (3.06) n=15	10.16 (-0.22, 20.54), p=0.055
Gender	Male N=21	6.38 (0) n=9	2.18 (4.55) n=12	4.21 (-14.35, 22.76), p=0.640
	Female N=38	9.04 (3.56) n=22	2.65 (1.53) n=16	6.39 (-1.98, 14.75), p=0.130

¹ Unadjusted parametric t-test, ² P-values should not be used for statistical inference due to lack of multiplicity adjustments and potential inflation of type-I error rates.

Source: Reviewer Table

Need for Anti-pseudomonal therapy and other endpoints related to efficacy

Supportive analyses in Study C2303 were limited due to the small sample size in which cases involving new antibacterial drug use or respiratory related hospitalization occurred. The proportion of patients requiring anti-pseudomonal antibacterial drugs in the comparisons in this study was very low at 6/62 (9.7%) and was similar between the TIP and placebo arms at 3/32 (9.4%) vs. 3/30 (10.0%). However it should be noted that one patient with new antibacterial drug use in the TIP arm had mistakenly received placebo. Respiratory related hospitalizations were also rare in this study. Only one patient in the study (a placebo patient) had a respiratory related hospitalization during the course of this 8 week study.

FDA Conclusions Regarding Study C2303

While Study C2303 did not accrue the projected sample size, it failed to meet its primary endpoint. Additional sensitivity and supportive analyses also failed to show significance. Although there is a weak suggestion of a benefit from TIP therapy in terms of FEV₁ % predicted improvements based on numeric comparisons and graphical representations, the level of evidence presented from the primary analysis is not acceptable for drawing valid statistical inferences since the possibility of chance findings cannot be ruled out.

Study C2302

Study Design

Study C2302 was an open-label, comparative study over a 24 week period (3 cycles) consisting of 4 weeks of on-therapy (TIP vs. TOBI®) followed by 4 weeks of off-therapy. The study population included patients diagnosed with CF and presence of *Pseudomonas aeruginosa* (PA) who were 6 years and older, who had no exposure to inhaled anti-pseudomonal antibacterial drugs within 1 month prior to screening and had a screening FEV₁ % predicted between 25% and 75%.

Study Conduct

This study randomized a total of 553 patients from 127 sites to receive TIP (112 mg, 4x28mg capsules) via the T-326 dry powder inhaler or TOBI® (5 mL of a 60 mg/mL solution via the PARI LC Plus nebulizer and DeVilbiss PulmoAide compressor or suitable alternative) in a 3:2 ratio. Patients were enrolled between February 2006 and March 2009. The ITT Population included 517 patients from the following regions: North America (326 patients), Europe and rest of the world (175 patients) and Latin America (16 patients).

Primary Endpoint

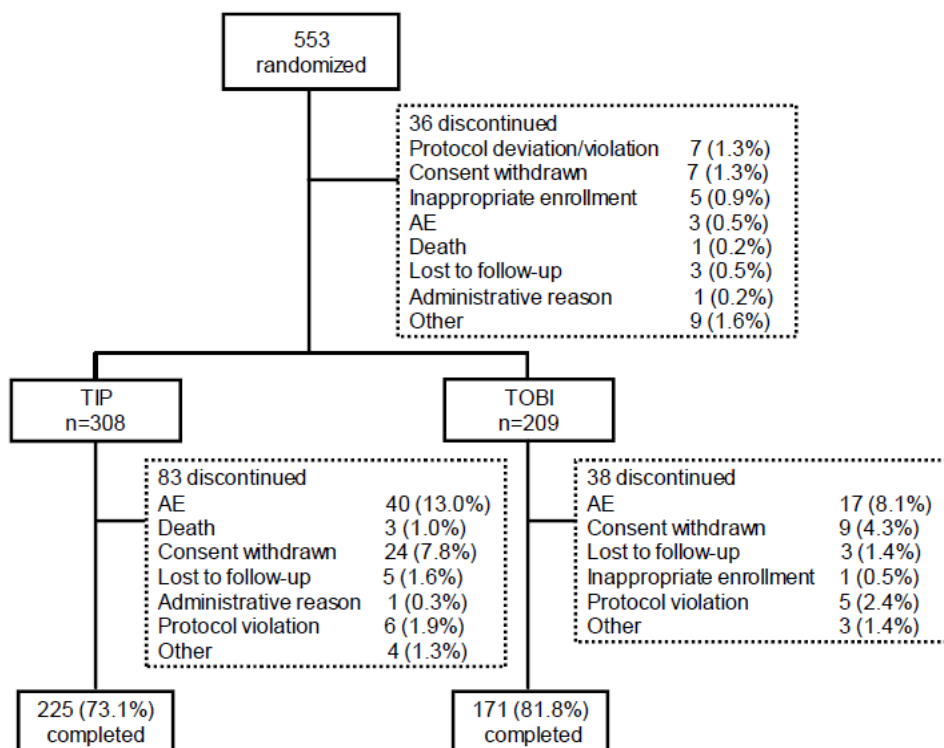
There was no pre-specified primary efficacy endpoint for this study. Secondary efficacy variables included spirometry measurements such as relative changes in FEV₁ % predicted

from baseline at all scheduled post-treatment visits (Weeks 2, 5, 9, 13, 17, 21 and 25), changes in PA density, changes in PA tobramycin minimum inhibitory concentration (MIC) susceptibility and time to first hospitalization due to a respiratory SAE. An additional secondary endpoint was the report of treatment satisfaction.

Analysis Population

The ITT (identical to the All Randomized Safety Population) was the main analysis population. The ITT included 308 patients in the TIP group and 209 patients in the TOBI® group. Of the 308 ITT patients, a larger percentage of discontinuations were observed in the TIP arm and a greater proportion of these discontinuations were attributed to adverse events (13.0% TIP vs. 8.1% TOBI®) as shown in FIGURE 9.

FIGURE 9
Subject Disposition (C2302 All Randomized) (submitted by the applicant to NDA 201,688)



Patients were generally balanced between the treatment groups with respect to baseline characteristics as shown. Compared to the placebo controlled studies which included patients between the ages of 6 and 21 years, Study C2302 included much older patients with a mean (median) age of 25.9 (24.0) years where over 69% of the ITT population was over 20 years of age and less than 9% of patients were under 13 years of age. Four patients enrolled in the study were over 70 years of age. An information request to the applicant regarding these older patients is presently pending.

TABLE 14
Baseline Characteristics (C2302 ITT)

Variable		ITT Population (N=517)	
		TIP (N=308)	TOBI® (N=209)
Age group; n (%)	≥ 6 yrs to < 13 yrs	28 (9.1)	19 (9.1)
	≥ 13 yrs to ≤ 20 yrs	66 (21.4)	47 (22.5)
	≥ 20 yrs	214 (69.5)	143 (68.4)
Gender n (%)	Male	171 (55.5)	115 (55.0)
	Female	137 (44.5)	94 (45.0)
Race	Caucasian	279 (90.6)	189 (90.4)
	Other	29 (9.4)	20 (9.6)
Region	North America	195 (63.3)	131 (62.7)
	Europe and rest of world	104 (33.8)	71 (34.0)
	Latin America	9 (2.9)	7 (3.3)
Severity; n (%)¹	FEV1 % pred < 50%	128 (41.6)	89 (42.6)
	FEV1 % pred ≥ 50%	180 (58.4)	120 (57.4)
Age (years)	Mean ± SD (Median)	25.9 ± 11.36 (24.0)	25.2 ± 10.20 (24.0)

¹ Screening FEV1 % predicted value. If missing, baseline FEV1 % predicted value used.

Source: Reviewer Table

Sustainability of Relative Changes in FEV1 % Predicted

Patients in Study C2302 received three 8 week cycles (24 weeks) of on/off therapy where each cycle consisted of 4 weeks of on-therapy (TIP vs. TOBI®) followed by 4 weeks off-therapy. This design allows for treatment comparisons of longer term efficacy (TIP vs. TOBI®) based on relative changes from baseline in FEV1 % predicted at several time points throughout the 24 week period. This design also allows for comparisons of relative changes across time points within each of the treatment arms. However, there were two factors which limited the strength of between treatment comparisons and within treatment comparisons over time.

One factor was higher rates of missing data at later visits following the on-therapy period of the first cycle at Week 5 (i.e. at visits between Week 9 to Week 21). Another factor was that FEV1 % predicted was that relative improvements at Week 25 (i.e. the follow-up visit at the end of the study) were measured in a different manner from all other post-baseline visits. These factors are discussed further in the ‘Sustainability of Relative Changes in FEV1 % Predicted’ section of Study C2301

TABLE 15
Number (%) of Patients (%) with Missing FEV1 % Predicted Measurements by Visit (C2302 ITT)

Visit ending:	TIP (N=308)	TOBI® (N=209)
Week 2	17 (5.5%)	14 (6.7%)
Week 5	40 (13.0%)	15 (7.2%)
Week 9	41 (13.3%)	25 (12.0%)
Week 13	56 (18.2%)	31 (14.8%)
Week 17	69 (22.4%)	34 (16.3%)
Week 21	81 (26.3%)	38 (18.2%)
Week 25	30 (9.7%)	8 (3.8%)

Source: Reviewer Table

The second factor limiting an evaluation of the sustainability of relative changes in FEV1 % predicted was that relative improvements at Week 25 (i.e. the follow-up visit at the end of the study) were measured in a different manner from all other post-baseline visits. The Week 25 visit had measured FEV1 % predicted measurements as ‘routine’ while all other visits had taken measurements both pre-dose and 30 minutes post-dose. Applicant (and reviewer) analyses had considered relative improvements from baseline in FEV1 % predicted based on pre-dose measurements. The lack of available pre-dose measurements at Week 25 may confound comparisons of relative changes with earlier time points due to differences in study conduct. Consideration of visits only up to Week 21 where FEV1 % predicted was measured based on pre-dose measurements greatly reduces the available information concerning a potential trend. This is because only two (rather than three) complete cycles can be used in comparing treatment differences or trends over time within a treatment.

In TABLE 16 and FIGURE 10, the mean relative change from baseline in FEV1 % predicted for TIP patients at Week 2 of 6.77% dropped substantially to 2.46% by Week 5 and dropped further to -0.52% by Week 9 following the off-therapy period. In the second and third cycle, the mean relative change remained at lower levels in a range between -0.24% and 2.28%. Mean relative changes in TOBI® patients at Week 2 were also at 6.80% and dropped by Weeks 5 & 9 with relative changes of 3.33% and 0.52%, respectively. In the second and third cycle, the mean relative changes were in a range between -1.99% and 3.67%.

In TABLE 16 and FIGURE 10, the mean relative change from baseline in FEV1 % predicted for TIP patients of 6.8% at Week 2 dropped substantially at Week 5 to 2.5%, and dropped further following the off-therapy period at Week 9 to -0.5%. In the second and third cycle, the mean relative change remained at lower levels in a range between -0.2% and 2.3%. Mean relative changes in TOBI® patients starting Week 2 were also at 6.8% and dropped by the start of Weeks 5 & 9 with relative changes of 3.3% and 0.5%, respectively. In the second and third cycle, the mean relative changes were in a range between -2.0% and 3.7%.

Overall, TOBI® patients fared slightly better than TIP patients over the first two cycles but slightly worse by the end of the third cycle (Week 25). However, as noted above, the end of study visit starting Week 25 did not measure FEV1 in the same manner as in previous visits (i.e. at pre-dose) and may not provide reliable data for comparing treatment means or changes in FEV1 % predicted over time within a treatment arm.

TABLE 16
Reviewer's Analysis of Sustainability of Relative Changes from Baseline in FEV1 % Predicted at All Visits Using Imputed Data (C2302 ITT)

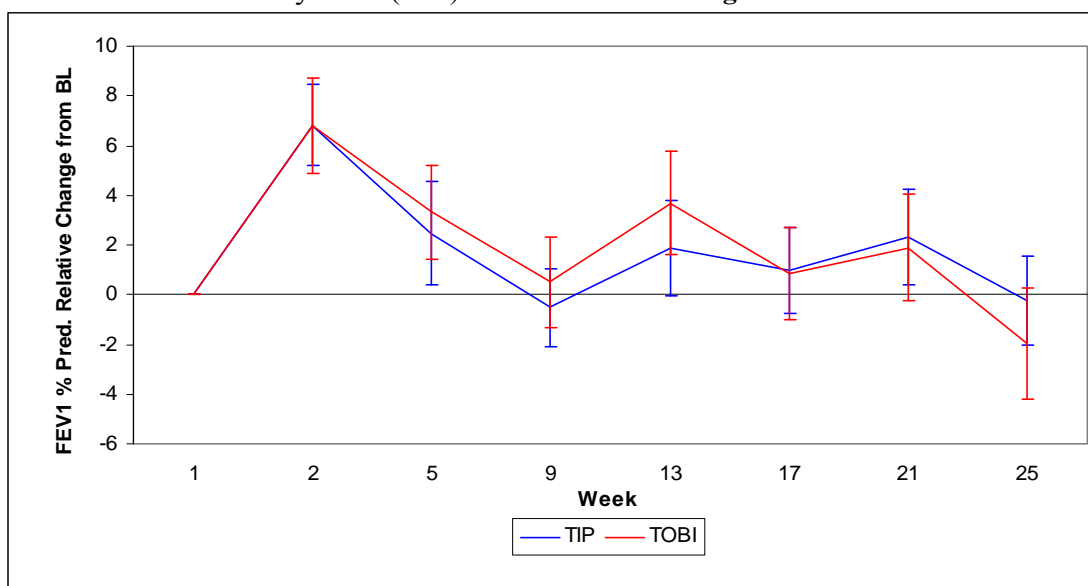
Visit starting:	TIP N=308 Mean (Median)	TOBI® N=209 Mean (Median)	Mean Treatment Difference: TIP-TOBI® (SE)	95% CI for Mean Difference	P-value
Week 2	6.77 (4.47)	6.80 (3.77)	-0.02 (1.30)	(-2.57, 2.53)	p=.987 ¹ p=.898 ²
Week 5	2.46 (0.00)	3.33 (1.98)	-0.87 (1.49)	(-3.80, 2.07)	p=.561 ¹ p=.164 ²
Week 9	-0.52 (-0.52)	0.52 (-0.52)	-1.04 (1.22)	(-3.44, 1.36)	p=.395 ¹ p=.324 ²
Week 13	1.87 (0.00)	3.67 (0.00)	-1.80 (1.47)	(-4.69, 1.08)	p=.219 ¹ p=.055 ²
Week 17	0.99 (0.00)	0.82 (0.00)	0.16 (1.32)	(-2.44, 2.77)	p=.901 ¹ p=.863 ²
Week 21	2.28 (0.00)	1.90 (0.00)	0.38 (1.49)	(-2.55, 3.32)	p=.798 ¹ p=.736 ²
Week 25	-0.24 (-1.99)	-1.99 (-2.34)	1.75 (1.44)	(-1.09, 4.59)	p=.227 ¹ p=.247 ²

¹ Parametric t-test, ² Nonparametric Wilcoxon Rank Sum test

Source: Reviewer Table

FIGURE 10

Study C2302- Mean FEV1 % Predicted Relative Changes from Baseline with 95% Confidence Limits by Visit (ITT) Source: Reviewer Figure



Subgroup Analyses

Relative changes from baseline in FEV1 % predicted were highly dependent upon the region considered with substantially larger improvements in European vs. US sites, especially for patients in the TOBI® arm (TABLE 17). Relative changes also depended on the age group of patients considered with larger relative changes occurring in younger patients (TABLE 18). There was also a dependence of relative changes on baseline FEV1 % predicted ($\geq 50\%$ vs. $< 50\%$), with larger relative changes occurring in patients with baseline FEV1 % predicted $< 50\%$ (TABLE 19). A further dependence was observed based on gender with larger relative improvements observed in male patients (TABLE 20).

In these subgroup analyses where sample sizes were relatively large, each subgroup division was analyzed independently with missing data imputed based on the minimum of 0 and the least favorable group mean at each visit, using only patients within that subgroup division. For example, patients from Europe with missing data in the subgroup analysis by region would have their missing data imputed using only subjects from Europe with observed relative changes.

In the subgroup analysis by region (TABLE 17), changes in FEV1 % predicted were substantially higher in Europe vs. the US. For the US region, relative changes were generally similar between TIP and TOBI® patients, except for the end of study visit (Week 25) where TOBI® patients experienced a substantial drop following their third course of therapy. However, the treatment difference at Week 25 was not significant ($p=0.092$). For the region of Europe, changes in FEV1 % predicted appeared to favor TOBI® over TIP, especially during the first two cycles. Using a non-parametric Wilcoxon rank sum test, treatment differences approached significance at several time points. For example, p -values for observed treatment differences at Week 9, Week 13, Week 17 were $p=.090$, $p=.081$, $p=.096$. It is also notable that changes in FEV1 % predicted following the end of on-therapy measurements (TABLE 17, shown in **bold**) tended to be substantial for patients in Europe (esp. for TOBI® patients) but were small or negligible in patients in the US, ranging from only 0.34% to 0.91% in TIP patients and -0.38% to 1.97% in TOBI® patients.

TABLE 17

Subgroup Analyses of Relative Changes from Baseline in FEV1 % Predicted at All Visits by Region Using Imputed Data (C2302 ITT)

Mean (Median) Relative Change from Baseline in FEV1 % Predicted:						
Region ³	US (N=326)			Europe (N=175)		
Visit	TIP (N=195)	TOBI® (N=131)	Mean Diff: TIP–TOBI® (SE)	TIP (N=104)	TOBI® (N=71)	Mean Diff: TIP–TOBI® (SE)
Week 2	5.72 (3.57)	5.99 (3.06)	-0.27 (1.54)	8.01 (5.53)	8.98 (5.33)	-0.98 (2.43)
Week 5	0.46 (0)	1.40 (0)	-0.94 (1.64)	4.41 (0)	6.81 (2.73)	-2.40 (2.77)
Week 9	-1.06 (-1.06)	-0.88 (-0.52)	-0.18 (1.43)	-0.74 (-0.74)	1.95 (0)	-2.69 (2.16) ³
Week 13	0.91 (0)	1.97 (0)	-1.07 (1.70)	2.76 (0)	6.77 (1.90)	-4.01 (2.77)³
Week 17	0.52 (-0.73)	-0.73 (0)	1.24 (1.52)	0.76 (0)	3.06 (1.64)	-2.30 (2.50) ³
Week 21	0.34 (-0.38)	-0.38 (0)	0.72 (1.69)	4.02 (0)	5.37 (0.95)	-1.35 (2.61)
Week 25	-1.29 (-4.00)	-4.00 (-2.82)	2.81 (1.66) ⁴	0.61 (0)	1.23 (-1.94)	-0.62 (2.76)

¹ P-values for the treatment difference favoring TOBI® at Week 9, Week 13, Week 17 were p= .090, p=.081, p=.096 using a rank sum test.

² P-value of 0.092 using a t-test.

³ Sixteen patients from Latin American sites are not shown in this table.

FEV1 % predicted measurements at end of on-therapy periods are shown in **bold**.

Source: Reviewer Table

In the subgroup analysis by age (TABLE 18), changes in FEV1 % predicted were highest in the younger age groups with patients in the 6 to 12 age group experiencing the largest relative improvement and patients in the 12 to 19 age group experiencing the next large relative improvement. In the 6 to 12 age group, mean (median) estimates were highly variable due to small sample sizes and could not be observed to consistently favor either treatment arm. For the 13 to 19 age group, relative improvements were substantially smaller than the 6 to 12 age group, especially at later study visits, but tended to slightly favor TIP over TOBI® over most visits. For the 20 and above age group, relative changes were much lower than in the two younger age groups and tended to slightly favor the TOBI® arm. It is also notable that changes in FEV1 % predicted following the 3 end of on-therapy measurements (TABLE 18, shown in **bold**) tended to be substantial in patients under the age of 20 but were small or negligible in patients 20 years or older, ranging from only 0.19% to 0.49% in TIP patients and 0.70% to 2.24% in TOBI® patients.

TABLE 18

Subgroup Analyses of Relative Changes from Baseline in FEV1 % Predicted at All Visits by Age Group Using Imputed Data (C2302 ITT)

Mean (Median) Relative Change from Baseline in FEV1 % Predicted:						
Age Group	6 to 12 Years (N=47)		13 to 19 Years (N=113)		≥ 20 Years (N=357)	
Visit	TIP (N=28)	TOBI® (N=19)	TIP (N=66)	TOBI® (N=47)	TIP (N=214)	TOBI® (N=143)
Week 2	9.73 (10.72)	12.51 (11.54)	11.21 (9.85)	9.21 (6.09)	5.02 (2.77)	5.24 (3.06)
Week 5	6.30 (1.27)	11.59 (7.14)	7.33 (4.42)	4.30 (2.65)	0.45 (0)	1.91 (0.85)
Week 9	0.90 (1.37)	10.86 (8.62)	1.17 (0)	0.36 (0)	-1.35 (-1.35)	-0.88 (-1.35)
Week 13	3.72 (-0.59)	11.27 (7.69)	5.56 (0)	4.96 (2.56)	0.49 (0)	2.24 (0)
Week 17	7.86 (7.66)	5.99 (0.50)	2.71 (0.21)	2.04 (0)	-0.61 (-0.61)	-0.36 (-0.61)
Week 21	10.36 (6.34)	8.73 (5.75)	5.64 (3.18)	2.79 (0.55)	0.19 (0)	0.70 (0)
Week 25	9.48 (8.20)	6.69 (6.96)	2.88 (1.65)	0.77 (0)	-2.65 (-4.08)	-4.08 (-4.08)

FEV1 % predicted measurements at end of on-therapy periods are shown in **bold**.

Source: Reviewer Table

In the subgroup analysis by baseline FEV1 % predicted ($\geq 50\%$ vs. $< 50\%$) (TABLE 19), changes in FEV1 % predicted were highest in patients with baseline FEV1 % predicted $< 50\%$, especially among TIP patients. Treatment means within each of the ' $\geq 50\%$ ' and ' $< 50\%$ ' subgroup divisions were generally similar. However, relative changes in TIP patients appeared to more sensitive to a change in baseline FEV1 % predicted category (i.e. $\geq 50\%$ vs. $< 50\%$). Among TIP patients, mean relative changes in FEV1 % predicted following on-therapy periods (shown in **bold**) were approximately 3.2% to 3.5% greater for patients with a baseline FEV1 % predicted of $< 50\%$ vs. a baseline FEV1 % predicted of $\geq 50\%$.

TABLE 19

Subgroup Analyses of Relative Changes from Baseline in FEV1 % Predicted at All Visits by Disease Severity: FEV1 % Predicted at Baseline ($\geq 50\%$ vs. $< 50\%$) Using Imputed Data (C2302 ITT)

Mean (Median) Relative Change from Baseline in FEV1 % Predicted:						
Baseline FEV1 % Predicted:	$\geq 50\%$ (N=300)			$< 50\%$ (N=227)		
Visit	TIP (N=180)	TOBI® (N=120)	Mean Difference (SE)	TIP (N=128)	TOBI® (N=189)	Mean Difference (SE)
Week 2	5.66 (3.68)	5.01 (3.63)	0.66 (1.47)	8.33 (6.63)	9.21 (5.26)	-0.88 (2.31)
Week 5	1.00 (0)	3.24 (2.28)	-2.24 (1.68)	4.50 (0)	3.44 (1.82)	1.06 (2.69)
Week 9	-1.11 (-1.11)	-0.84 (-1.11)	-0.26 (1.44)	0.31 (0)	2.34 (0)	-2.03 (2.12)
Week 13	0.53 (0)	2.58 (0)	-2.04 (1.65)	3.75 (0)	5.16 (0)	-1.41 (2.64)
Week 17	0.49 (-0.03)	-0.03 (-0.03)	0.52 (1.45)	1.68 (0)	1.96 (0)	-0.29 (2.44)
Week 21	0.96 (0)	1.02 (0)	-0.06 (1.71)	4.15 (0)	3.09 (0)	1.06 (2.65)
Week 25	0.14 (-2.87)	-3.24 (-3.24)	3.39 (1.77) ¹	-0.62 (-0.62)	-0.26 (-2.03)	-0.36 (2.43)

¹P-value for mean difference was 0.056 using t-test. FEV1 % predicted measurements at end of on-therapy periods are shown in **bold**.

Source: Reviewer Table

In the subgroup analysis by gender (male vs. female) in TABLE 20, changes in FEV1 % predicted were highest in male patients, especially among TOBI® patients. Mean relative changes in FEV1 % predicted following on-therapy periods (shown in **bold**) at Weeks 5, 13, 21 were 1.7% to 3.3% greater in females vs. males among TIP patients and 2.7% to 4.7% greater in males vs. females among TOBI® patients. Treatment means within each of the male and female subgroups were generally similar. In male patients, differences numerically favored TOBI® patients at Weeks 9 & 13, but were not statistically significant (i.e. $p=.128$ & $p=.060$).

TABLE 20

Subgroup Analyses of Relative Changes from Baseline in FEV1 % Predicted at All Visits by Gender Using Imputed Data (C2302 ITT)

Mean (Median) Relative Change from Baseline in FEV1 % Predicted:						
Gender	Male (N=286)			Female (N=231)		
Visit	TIP (N=171)	TOBI® (N=115)	Mean Difference (SE)	TIP (N=137)	TOBI® (N=94)	Mean Difference (SE)
Week 2	7.83 (6.19)	7.41 (5.26)	0.42 (1.73)	5.45 (3.76)	6.04 (3.05)	-0.59 (1.96)
Week 5	3.88 (0)	4.94 (2.66)	-1.06 (2.18)	0.68 (0)	1.35 (0)	-0.67 (1.95)
Week 9	0.01 (0)	2.38 (0.33)	-2.37(1.68) ¹	-1.34 (-1.94)	-1.94 (-1.94)	0.61 (1.77)
Week 13	2.61 (0)	5.80 (1.72)	-3.19 (2.09)²	0.94 (0)	1.08 (0)	-0.13 (2.01)
Week 17	1.90 (0)	1.93 (0)	-0.03 (1.96)	-0.29 (-0.69)	-0.69 (-0.69)	0.39 (1.70)
Week 21	3.75 (0)	3.11 (0)	0.65 (2.16)	0.45 (0)	0.43 (0)	0.02 (1.99)
Week 25	0.32 (-1.44)	-1.44 (-2.90)	1.76 (2.08)	-0.96 (-2.67)	-2.67(-2.67)	1.70 (1.96)

Source: Reviewer Table

1 P-value for treatment difference was 0.128 using rank sum test.

2 P-value for treatment difference was 0.060 using rank sum test.

FEV1 % predicted measurements at end of on-therapy periods are shown in **bold**.

Compliance

No advantage in compliance was demonstrated for TIP in this comparative study. This is discussed further in the Compliance and Device Useability section of this briefing document.

Patient Satisfaction

The applicant administered a Treatment Satisfaction Questionnaire for Medication (TSQM) to evaluate patient opinions on such issues as effectiveness, side effects, and convenience of TIP in comparison to TOBI®. Satisfaction was assessed at the end of each on cycle period. The original questionnaire consisted of 14 questions with responses rated on a 5 or 7 point scale; however, the applicant added 4 questions to the original 14 questions and also adjusted some wording.. These questions were divided into four domains described as side effects, convenience, and global satisfaction. Each question had a range of possible answers which varied slightly in detail and number from question to question (not at all certain to extremely certain, extremely difficult to extremely easy, a great deal to not at all, etc.). The TSQM has been validated in the scientific literature; The TSQM with the modifications was not re-validated.

The results of this survey show statistically higher satisfaction in the TIP arm, particularly in the areas of convenience, effectiveness, and global satisfaction. However, it can be difficult to draw a relationship between treatment satisfaction and clinical results. An example of this is illustrated below with question 13 of the questionnaire:

How certain are you that the good things about your medication outweigh the bad things?

1. Not at all certain 2. A little certain 3. Somewhat certain 4. Very Certain 5. Extremely certain

In the TIP arm, 229 subjects (74%) reported a score of 4 or above on the above question at any point in the study. 69 (30%) of these 229 subjects had an SAE. 69 subjects (22%) ever reported a score of 2 or below. 19 (28%) of these 69 subjects had an SAE. In the TOBI® arm, 166 subjects (79%) reported a score of 4 or above at any point in the study. 48 (29%) of these 166 subjects had an SAE. In the TOBI® arm 27 subjects (13%) ever reported a score of 2 or below. 6 (22%) of these 27 subjects had an SAE. Although the survey results may indeed point to increased satisfaction with TIP compared to TOBI®, challenges remain with the interpretation of these results for at least some questions or domains.

Need for Anti-pseudomonal Antibacterial Use and other efficacy related endpoints

Exploratory/other analyses in Study C2302 of interest were the rates of antibacterial drug use and respiratory related hospitalization over the 3 cycles. The proportion of patients requiring new anti-pseudomonal antibacterial drugs in this study was significantly higher in the TIP vs. the TOBI® arm at 200/308 (64.9%) vs. 114/209 (54.5%), p=0.018. However, rates of respiratory related hospitalizations were similar between the treatment arms (i.e. only slightly higher in TIP arm).

TABLE 21

Other Analyses: Antibacterial Drug Use, Respiratory Related Hospitalization (C2302 ITT)

	TIP (N=308)	Placebo (N=209)	Treatment Difference (95% CI), p-value
New Antibacterial Drug Use	200 (64.9%)	114 (54.5%)	10.4% (1.8%, 18.9%), p=0.018
Respiratory Related Hospitalization	75 (24.4%)	46 (22.0%)	2.3% (-5.2%, 9.6%), p=0.537

Source: Reviewer Table

FDA Conclusions Regarding Study C2302

In this open-label study, a larger percentage of discontinuations were observed in the TIP arm and a greater proportion of discontinuations were attributed to adverse events (13.0% TIP vs. 8.1% TOBI®). FEV1 % predicted comparisons generally favored TOBI®. At end of Cycle 2 (Week 25), the treatment difference favored TOBI® and bordered upon statistical significance in the reviewer's analyses using the Wilcoxon Rank Sum test (p=0.055). This finding was also supported by findings of rates of new use of anti-pseudomonal antibacterial drugs where treatment differences were significantly favored TOBI® over TIP (i.e. 64.9% for TIP vs. 54.5% for TOBI®, p=0.018).

For both TIP and TOBI®, improvements from baseline in FEV1 % predicted were modest during the on-therapy period and were substantially reduced during the off-therapy period. In TIP patients, both mean and median FEV1 % predicted measurements dropped below their baseline levels following the first cycle of on/off therapy. It should be noted that evaluation of the sustainability of improvements was limited by two factors: 1) high rates of missing data which varied across visits and tended to be greater in TIP patients and 2) differences in study conduct across visits (e.g. Week 25 visit measured FEV1 % ‘at visit’ rather than ‘pre-dose’ at all other visits).

Differences in rates of missing data made treatment comparisons challenging. Reviewer analyses imputed missing data using the minimum of 0 and the least favorable group mean, however, it is not clear as to whether such an imputation would be conservative enough to account for the imbalance in treatment groups with respect to discontinuation rates, especially for discontinuations due to adverse events.

The study did not demonstrate improved compliance for TIP vs. TOBI®, but there was statistically higher patient satisfaction assessed by questionnaire for TIP.

Safety

Safety in Phase 1

Repeat-dose and dose-ranging studies assessed the safety of TIP first in healthy volunteers (INH007) and in patients with cystic fibrosis (Phase 2 study: TPI-001) to inform dosing recommendations for TIP and compare safety to TOBI.

INH-007

This phase 1 study compared the lung deposition of serial single vs multiple (6) inhalations in one sitting of TIP to that achieved with TOBI. Multiple inhalations of TIP did not result in a greater rate of adverse events compared to a single inhalation of TIP, leading to the decision to inhale twice from each of the 4 capsules that comprise a single dose of TIP. The applicant reports the incidence of treatment emergent adverse events (TEAE) with single vs multiple inhalations of TIP to be 12% and 8%, respectively, compared to 3% with TOBI®.

TPI-001

This phase 1 study was designed to assess the safety of ascending single doses of TIP (28 mg to 112 mg) to define a dose to move forward in phase 3 and compare safety to TOBI. The applicant reports more subjects in the TIP arm to have had a TEAE (61% with TIP vs. 30% with TOBI) and drug related TEAEs (24/66 or 36.4% with TIP vs 2/20 or 10% with TOBI). Within the TIP arm, the TEAE rate increased with increasing dose. Serious TEAE, discontinuation due to a TEAE and AEs requiring treatment modification occurred in the TIP arm.

Safety in Placebo-controlled Phase 3 studies (C2301 and C2303)

The placebo controlled safety of TIP was characterized in the first cycle of treatment in Study C2301 and in C2303; placebo consisted of the inactive excipients in the TIP capsule formulation. Both placebo and TIP AE rates were numerically lower in 2303 compared to 2301. The placebo AE rate was 75.5% (37/49) compared to 50 % (23/46) for TIP in Cycle 1 of 2301; whereas the placebo AE rate was 34.4% (11/32) compared to 26.7 % (8/30) for TIP in 2303. Pure tone audiometry at baseline and post-treatment was performed in a subset of subjects in Study C2303. The limitation of this testing is that high frequency hearing loss characteristic of aminoglycoside mediated toxicity was not tested, and there were no prespecified criteria for significance in the changes in audiogram measurements over time. In the FDA analysis, 2 subjects in the TIP arm and none in the placebo arm met the American Academy of Audiology criteria of severe ototoxic change that requires either: (a) ≥ 20 dB decrease at any one test frequency, (b) ≥ 10 dB decrease at any two adjacent frequencies, or (c) loss of response at three consecutive frequencies where responses were previously obtained.²

Safety in the Comparative Phase 3 Study (C2302)

Subjects in Study C2302 serve as the primary safety population in the safety analysis. The rationale for this choice is consistent with the applicant's proposed indication for the use of TIP as an alternative to TOBI® for CF patients with *Pseudomonas* infection. The C2302 trial had a much larger safety database than either of the placebo-controlled trials; allowing detection of serious AEs occurring at a rate of 1% per treatment arm. In addition, the C2302 trial compared TIP to TOBI® over three successive on/off cycles while comparisons with placebo took place over only one on/off cycle. This longer duration of drug exposure permits an assessment of safety trends and signals over time to better characterize their significance. The placebo used in both C2301 and C2303 was a powder containing the same excipients present in the TIP powder minus the active ingredient-tobramycin sulfate; Study C2302 compares safety related to the use of an inhaled powder to a nebulized solution; this is clinically relevant given the current approved usage of only nebulized tobramycin (TOBI®) and nebulized aztreonam (Cayston) for similar indications in the United States.

Of note, the C2302 trial design included an open label comparison of TIP with an active comparator (nebulized tobramycin or TOBI®), a three cycle 28 day on/off regimen, and more liberal inclusion criteria that allowed for older subjects (mean age 25.9 yrs) and subjects recently using inhaled anti-pseudomonals (only needed to be off for 28 days prior to study). This was a multinational trial conducted in three primary regions- North America, Europe, and Latin America.

² American Academy of Audiology Position Statement and Clinical Practice Guidelines. Ototoxicity Monitoring. October 2009, American Academy of Audiology, URL: <http://www.audiology.org/resources/documentlibrary/Documents/OtoMonPositionGuideline.pdf>

Demographics of the Safety Population

The All Randomized Safety population was 517 subjects, 308 in the TIP arm and 209 in the TOBI® arm. However, there were significant numbers of discontinuations in both arms, particularly in the TIP arm, and all safety interpretations should be viewed within that context.

The subjects were well matched for age, sex, region, race, and baseline FEV1% predicted. However, it should be noted that 69% of the population was greater than 20 years of age, and 20% of patients in the TIP arm and 19% of patients in the TOBI® arm were older than the average life expectancy of CF patients. As noted above, there were four patients over 70 years in the enrolled population and an information request to the applicant is pending. There was a slightly increased percentage of patients in the TOBI® arm who had never used anti-pseudomonal antibacterial drugs prior to first study dose (4.6% of subjects TIP vs. 9.1% of subjects TOBI®).

Deaths

There were 3 deaths that occurred on the TIP arm compared to none in the TOBI® arm.

The first subject was a 24 year old female with a history of cystic fibrosis, diabetes mellitus, and repeated pulmonary exacerbations who developed a respiratory infection during the 2nd on cycle requiring treatment with meropenem and vancomycin. One month later the subject again developed signs and symptoms of pneumonia and was discontinued from study. She was hospitalized, given multiple anti-pseudomonal antimicrobial drugs, but continued to have a complicated course. Three weeks later she had continued respiratory decline, went into asystole and died.

The second subject was a 21 year old male with a history of chronic sinusitis and inhaled tobramycin use. During the 2nd off cycle, the subject had clinical signs of a pulmonary exacerbation (increased dyspnea, cough, sputum production) and was hospitalized and treated with multiple anti-pseudomonal drugs. He was hospitalized for four days, discharged but then readmitted again with similar symptoms four days later and again treated with multiple anti-pseudomonal drugs including meropenem, and piperacillin-tazobactam. The subject continued to deteriorate and died two weeks later.

The third subject was a 25 year old male with a history of diabetes, hydrocephalus with nonfunctioning CSF shunt, asthma, and multiple anti-pseudomonal courses in the year prior to study initiation. During the off period of cycle 1, subject started exhibiting signs and symptoms of pulmonary exacerbation (dyspnea, cough, etc.) and eventually was hospitalized for 10 days and treated with ciprofloxacin and colistin. Four days after finishing the 2nd on cycle, the subject again started having symptoms of pulmonary exacerbation and was hospitalized. He was treated with colistin, meropenem, and ciprofloxacin and was eventually discharged after 10 days. It is unclear if the subject ever restarted study drug. Three weeks after visit 9 (what would have been the beginning of 3rd on cycle study visit) the subject overdosed on a recreational drug and remained

unconscious for a prolonged period. This led to ischemic brain injury, mechanical ventilation, and aspiration pneumonia. He eventually succumbed 3 weeks after the recreational drug overdose.

We note that two of these deaths are attributable to pulmonary exacerbations.

Hospitalizations

The applicant reports a similar number of subjects in each arm who were hospitalized due to a respiratory-related event (TIP 24% and TOBI® 22%; All Randomized Safety Population). Similar results were found upon Agency review. In this analysis, using keywords that would have indicated a respiratory illness, the rate of respiratory related hospitalization was 25% in both the TIP and TOBI® arms. Time to hospitalization was noted to be 199 days in the arm TIP and 190 days in the TOBI® arm.

Overall Adverse Events

There was a higher incidence of adverse events in the TIP group overall and by cycle, particularly in cycles 1 and 3. In the TIP arm, 90.3% of subjects reported an adverse event vs. 84.2% of subjects in the TOBI® arm. We note that the rates in both arms would be altered if discontinuations are taken into account and counted as subjects with AEs. The discontinuation rate (see below) was greater in TIP than TOBI®.

System Organ Classes (SOCs) which had at least a 4% higher incidence of AEs in the TIP arm relative to the TOBI® arm were the Respiratory, thoracic, and mediastinal disorders SOC; General disorders and administration site conditions SOC, and Nervous system disorders SOC (TABLE 22). Please note the applicant table below. For the Respiratory, thoracic, and mediastinal disorders SOC, the preferred terms (PTs) of ‘cough,’ ‘lung disorder,’ ‘dyspnea,’ ‘oropharyngeal pain,’ ‘dysphonia,’ ‘throat irritation,’ ‘dyspnea exertion,’ and ‘nasal mucosa disorder’ drove the disparity. For the General disorders and administration site conditions SOC, the differences were noted in the PTs ‘pyrexia’ and ‘chest discomfort.’ For the nervous system SOC, the disparity was driven by the PT ‘dysgeusia.’

TABLE 22
Adverse Events by SOC and Treatment Group, All Randomized Safety population
(submitted by the applicant to NDA 201,688)

SOC	TIP N= 308	TOBI® N=209
Respiratory, thoracic and mediastinal disorders	246 (80%)	141 (68%)
General disorders & administrative site conditions	93 (30%)	45 (22%)
Nervous system disorders	65 (21%)	34 (16%)

-% reflect percentages of all randomized safety population

Considering individual PTs, those whose incidence was at least 2% higher in the TIP arm relative to the TOBI® arm were ‘diarrhea,’ ‘pyrexia,’ ‘chest discomfort,’ ‘forced expiratory volume decreased,’ ‘blood glucose increased,’ ‘dysgeusia,’ ‘cough,’ ‘lung

disorder,’ ‘oropharyngeal pain,’ ‘dyspnea,’ ‘dysphonia,’ ‘throat irritation,’ ‘dyspnea exertional,’ and ‘nasal mucosa disorder’. In the case of ‘cough’ and ‘dysphonia,’ the disparity was > 5%.

Treatment-Related Adverse Events

Overall, 51.0% of subjects in the TIP treatment group and 20.1% of subjects in the TOBI® group had AEs categorized as treatment-related . Preferred terms which occurred in the TIP arm at a rate $\geq 2\%$ higher than that of the TOBI® arm were ‘chest discomfort’ (3.2% TIP arm and 1.0% in the TOBI® arm), ‘dysgeusia’ (3.9% versus 0.5% in the TIP and TOBI® arms, respectively), ‘cough’ (25.3% in the TIP arm and 4.3% in the TOBI® arm), ‘dysphonia’ (12.7% in the TIP arm and 3.3% in the TOBI® arm), ‘dyspnea’ (5.5% versus 1.4% in the TIP and TOBI® groups, respectively), ‘oropharyngeal pain’ and ‘productive cough’ (both 4.5% in the TIP arm and 1.0% in the TOBI® arm), and ‘throat irritation’ (3.2% in the TIP arm and 1.0% in the TOBI® arm).

Evaluation of Specific Adverse Events

Candidiasis: Using the reported preferred terms of ‘vulvovaginal candidiasis,’ ‘vulvovaginal mycotic infection,’ ‘oropharyngeal candidiasis,’ ‘oral fungal infection,’ ‘oral candidiasis,’ ‘genital infection fungal,’ and ‘candidiasis,’ 13 (4.2%) subjects in the TIP arm and (3.4%) 7 subjects in the TOBI® arm had adverse events corresponding with such terms. If the preferred terms that specifically mention an oral candidal/fungal infection are used, 6 (1.9%) such subjects were noted in the TIP arm and none in the TOBI® arm.

Cough: Cough was reported as an AE in 48% of TIP patients and 31% of TOBI® patients. When analyzing this AE by subgroup, all age and baseline pulmonary function subgroups had more cough in the TIP arm relative to the TOBI® arm. Within the TIP arm, cough was reported more often in the youngest age group.

TABLE 23
Cough by Age and Pulmonary Function Subgroups and Treatment Arm

Study Drug	Age in Years n/N (%)			FEV1 % Predicted n/N (%)	
	≥ 6 to <13	≥ 13 to <20	≥ 20	≥ 25 <50%	$\geq 50\% \leq 75\%$
TIP	18/28 (64%)	36/66 (55%)	96/214 (45%)	61/128 (48%)	89/180 (49%)
TOBI®	4/18 (22%)	16/48 (33%)	49/143 (34%)	29/89 (33%)	40/120 (33%)

- PTs used for analysis were ‘cough,’ ‘productive cough,’ ‘upper airway cough syndrome,’ and ‘post-tussive vomiting,’

-denominators represent subgroups of All Randomized Safety population

Source: Reviewer Table

Including those cough events that were thought by the investigator/subject to be related to the study drug may separate cough events that may have occurred with drug administration from those cough events that were part of a pulmonary exacerbation (TABLE 24).

TABLE 24
Cough (Possibly or Probably Related) As a Function of Demographic Subgroups and Treatment Arm

	Age in Years			FEV1 % Predicted		Gender		Region		
n/N (%)	≥ 6 to <13	≥13 to <20	≥ 20	>25 to < 50%	≥50 to ≤75%	Female	Male	Eur.	LA	NA
TIP	11/28 (39)	18/66 (27)	50/214 (23)	34/128 (27)	45/180 (25)	41/137 (30)	38/171 (22)	26/104 (25)	1/9 (11)	52/195 (27)
TOBI	0/18 (0)	1/48 (2)	8/143 (6)	2/89 (2)	7/120 (6)	6/94 (6)	3/115 (3)	2/71 (3)	1/7 (14)	6/131 (5)

-PTs analyzed were 'cough,' 'productive cough,' 'upper airway cough syndrome' and 'post-tussive vomiting'

-Denominators represent subgroups of All Randomized Safety population

-Europe includes Israel and Australia, LA = Latin America, NA= North America

Source: Reviewer Table

Discontinuations

There were more discontinuations in the TIP arm than TOBI® arm (TIP 83 subjects [26.9%] and TOBI® 38 subjects [18.2%]). This disparity was driven by imbalances in discontinuations attributed to adverse events (TIP 14% vs. TOBI® 8.1%) and withdrawal of consent (TIP 7.8% and TOBI® 4.3%). Preferred terms where TIP arm discontinuation rates exceeded TOBI® by at least 2 subjects included 'cystic fibrosis lung,' 'chest discomfort,' 'pyrexia,' 'cough,' 'dyspnea,' 'bronchospasm,' 'dysphonia,' and 'throat irritation.'

TABLE 25
Subgroup Analysis of Study Discontinuations by Treatment Arm

	TIP n/N (%)	TOBI® n/N (%)
ALL	83	38
Sex		
Male	47/171 (27.5)	17/115 (14.8)
Female	36/137 (26.3)	21/94 (22.3)
Age		
≥6 to <13 years old	1/28 (3.6)	3/18 (16.7)
≥13 to < 20 years old	12/66 (18.2)	8/48 (16.7)
≥ 20 years old	70/214 (32.7)	27/143 (18.8)
Baseline pulmonary function		
< 50 % FEV1 % predicted	47/122 (38.5)	20/95 (21)
≥ 50 FEV1 % predicted	36/186 (19.4)	18/114 (15.7)
Region		
North America	52/195 (26.7)	28/131 (21.4)
Latin America	1/9 (11.1)	0/7 (0)
Europe	30/104 (28.8)	10/71 (14)

- percentages represent percentage of that particular demographic in the All Randomized Safety population

Source: Reviewer Table

When comparing TIP to TOBI®, all analyzed subgroups except for the youngest age group had higher rates of discontinuation within the TIP arm. Within the TIP arm, higher rates of discontinuation were seen in the eldest age group and in subjects with lower baseline pulmonary function. The profile of subjects who discontinued study drug permanently due to an adverse event but did not discontinue the study is similar.

FDA Conclusions Regarding Safety

Study C2302 was an open label comparison of TIP with an active comparator (nebulized tobramycin or TOBI®) with a three cycle 28 day on/off regimen. The safety population in Study C2302 included 517 subjects, 308 in the TIP arm and 209 in the TOBI® arm. There were 3 deaths that occurred on the TIP arm compared to none in the TOBI® arm, and two of these deaths are attributable to pulmonary exacerbations. A similar number of subjects in each arm were hospitalized due to a respiratory-related event. Local upper airway adverse events of dysphonia and dysgeusia were seen with greater frequency with TIP compared to TOBI®. Cough was reported as an AE in 48% of TIP patients and 31% of TOBI® patients. When analyzing the AE of cough by subgroup, all age and baseline pulmonary function subgroups had more cough in the TIP arm relative to the TOBI® arm, with the greatest difference seen in the youngest age group. There were more discontinuations in the TIP arm than TOBI® arm (TIP 83 subjects [26.9%] and TOBI® 38 subjects [18.2%]). This disparity was driven by imbalances in discontinuations attributed to adverse events (TIP 14% vs. TOBI® 8.1%) and withdrawal of consent (TIP 7.8% and TOBI® 4.3%).

Microbiology

***P. aeruginosa* Density in Sputum**

An important analysis in the Phase 3 studies was to demonstrate that TIP effectively suppressed *P. aeruginosa* in the lungs of CF patients, as demonstrated by reduced numbers of *P. aeruginosa* in sputum specimens.

Study C2301

P. aeruginosa concentration in sputum was measured at Day 1 and Day 28 for each of the three treatment cycles in study C2301. *P. aeruginosa* concentration results are summarized using a logarithmic scale as log₁₀ CFU per gram of sputum. Absolute changes from baseline to each post-baseline time point in each of the three cycles were summarized descriptively by treatment group and colony type (mucoid, dry, and small) of *P. aeruginosa* isolate. Changes in CFUs in all colony types are presented in TABLE 26.

TABLE 26

FDA's Analysis of Change from baseline in *P. aeruginosa* colony forming units (log₁₀ CFUs) in Study C2301 (ITT population—all colony types)

Study Cycle	week/day	Value	TIP/TIP/TIP				PLB/TIP/TIP			
			N=46				N=49			
			N	mean	SD	median	N	Mean	SD	median
Baseline		Raw value	44	7.04	(1.70)	7.60	48	7.17	(1.68)	7.59
Cycle 1	1/1	Raw value	37	7.15	(1.49)	7.59	40	7.55	(1.23)	7.77
	5/28	Raw value	28	4.60	(2.33)	4.28	37	7.30	(1.46)	7.53
		Change	28	-2.79	(2.59)	-3.04	36	-0.21	(1.29)	-0.10
Cycle 2	9/1	Raw value	31	6.56	(2.07)	7.16	32	7.29	(1.53)	7.36
		Change	31	-0.76	(1.96)	-0.49	32	-0.38	(1.79)	-0.22
	13/28	Raw value	26	4.75	(2.00)	4.56	23	4.49	(2.12)	3.75
		Change	26	-2.44	(2.25)	-2.22	23	-3.19	(2.46)	-3.85
		Change	26	-2.44	(2.25)	-2.22	23	-3.19	(2.46)	-3.85
Cycle 3	17/1	Raw value	30	6.85	(1.74)	7.63	28	6.67	(1.41)	6.93
		Change	30	-0.34	(1.76)	-0.19	28	-0.76	(1.80)	-0.66
	21/28	Raw value	24	5.47	(2.32)	5.01	24	4.42	(1.88)	4.00
		Change	24	-1.99	(2.67)	-1.87	24	-3.14	(2.22)	-3.26
		Change	24	-1.99	(2.67)	-1.87	24	-3.14	(2.22)	-3.26
Follow-up	25/56	Raw value	25	7.18	(1.38)	7.49	25	6.88	(1.60)	7.20
		Change	25	-0.29	(1.00)	-0.18	25	-0.91	(1.82)	-0.54
Termination visit		Raw value	40	6.20	(2.04)	6.68	43	6.31	(2.02)	7.00
		Change	40	-1.08	(1.91)	-0.54	42	-1.10	(2.45)	-0.57

Baseline was defined as the latest measurement prior to the first dosing of study medication.

Change = change from baseline.

Overall density is used, and it is defined as the sum of colony types (mucoid, dry and small colony variant). The log₁₀ is taken on the sum.

Termination visit: last available post-baseline measurement.

The greater value was chosen when subject had more than one measurement at the same visit date.

The later non-missing value was chosen when subject had more than one measurement at the same visit with different collecting date.

ITT population corresponds to the All Randomized Safety Population in C2301 CSR.

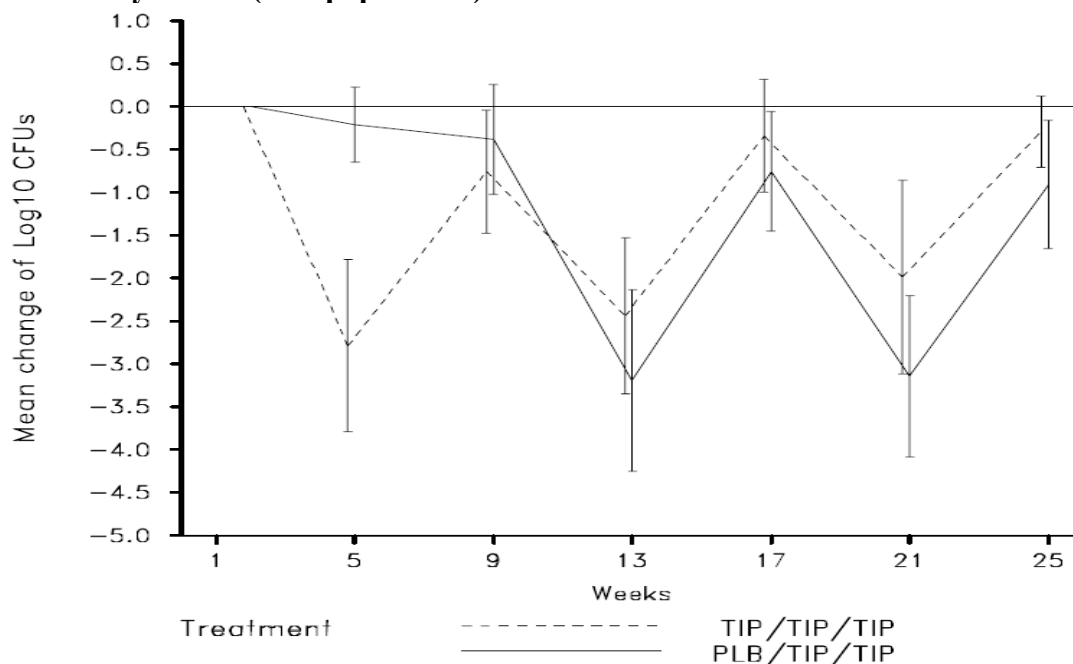
Source: Table 3.2-1.2a,NDA submission.

At the end of the first cycle of treatment (Week 5), the TIP arm (change shown in shaded gray) showed a greater reduction in CFUs than the placebo arm (-2.79 and -0.21 log₁₀ CFUs, respectively). At the end of cycle 2, where both arms received TIP, the reduction was lower in the TIP arm than the placebo arm that received its initial cycle of TIP (-2.44 and -3.19 log₁₀ CFUs, respectively). The log₁₀ reduction at the end of treatment cycle 3 compared to baseline colony types for *P. aeruginosa* CFUs was lower in the TIP arm than the placebo arm (-1.99 and -3.14 log₁₀ CFUs, respectively). This temporal trend of reduction in colony counts among all colony types combined, favored the test (TIP) arm only in the initial placebo-controlled cycle, but overall did not reduce the number of *P. aeruginosa* isolates more than the comparator arm. The log₁₀ reduction from the follow-up visit compared to baseline for all *P. aeruginosa* CFUs was similar in the TIP and the placebo arms (-0.29 and -0.91 log₁₀ CFUs, respectively), as was the case in the termination visit (-1.08 and -1.10 log₁₀ CFUs for the TIP and the placebo arms, respectively).

The effect of tobramycin treatments on concentrations of *P. aeruginosa* in sputum in Study 2301 is shown graphically in FIGURE 11.

FIGURE 11

Change from baseline in *P. aeruginosa* sputum concentration (Log₁₀ CFUs) in cycles 1 to 3 - Study C2301 (ITT population)



Note: the vertical bar is 95% confidence interval.

Overall density is used, and it is defined as the sum of bio-types (mucoid, dry and small colony variant).

Figure 4-6, Clinical Pharmacology Summary, NDA submission

The greatest difference between the TIP treatment group and the placebo groups is seen at Day 28 of Cycle 1 (a decrease of 2.79 log₁₀ CFUs in TIP group vs. 0.21 log₁₀ CFUs in placebo group).

Study C2302

The effect of the treatments on the concentration of *P. aeruginosa* in sputum in Study 2302 is shown in TABLE 27 and graphically in FIGURE 12.

TABLE 27
Change in *P. aeruginosa* colony forming units (log₁₀ CFUs) from baseline - Study C2302. (dry, mucoid and small colony types)

Study Cycle	week/ day	Value	TIP				TOBI®			
			N=308				N=209			
			N	mean	SD	median	N	mean	SD	median
Baseline		Raw value	279	7.23	1.49	7.64	192	7.35	1.54	7.68
Cycle 1	1/1	Raw value	248	7.24	1.46	7.63	170	7.47	1.50	7.88
	5/28	Raw value	204	5.60	1.84	5.40	148	6.29	1.89	6.36
		Change	202	-1.76	1.96	-1.60	145	-1.32	2.03	-1.00
Cycle 2	9/1	Raw value	204	7.01	1.75	7.42	146	7.14	1.66	7.68
		Change	203	-0.29	1.60	-0.14	144	-0.31	1.82	-0.16
	13/28	Raw value	181	5.83	1.76	5.88	130	6.43	1.77	6.60
		Change	179	-1.54	1.99	-1.46	125	-1.11	1.91	-0.85
Cycle 3	17/1	Raw value	190	6.95	1.78	7.29	136	7.30	1.64	7.92
		Change	187	-0.37	1.80	-0.16	131	-0.04	1.47	-0.01
	21/28	Raw value	158	5.69	1.88	5.40	129	6.59	1.72	6.81
		Change	157	-1.61	2.03	-1.40	126	-0.77	1.78	-0.67
Follow up	25/56	Raw value	167	6.84	1.82	7.24	135	7.33	1.51	7.93
		Change	165	-0.49	1.78	-0.38	130	-0.08	1.36	-0.14
Termination		Raw value	269	6.76	1.85	7.20	189	7.01	1.69	7.58
		Change	263	-0.53	1.92	-0.33	179	-0.33	1.71	-0.24

Baseline was defined as the latest measurement prior to the first dosing of study medication.

Change = change from baseline.

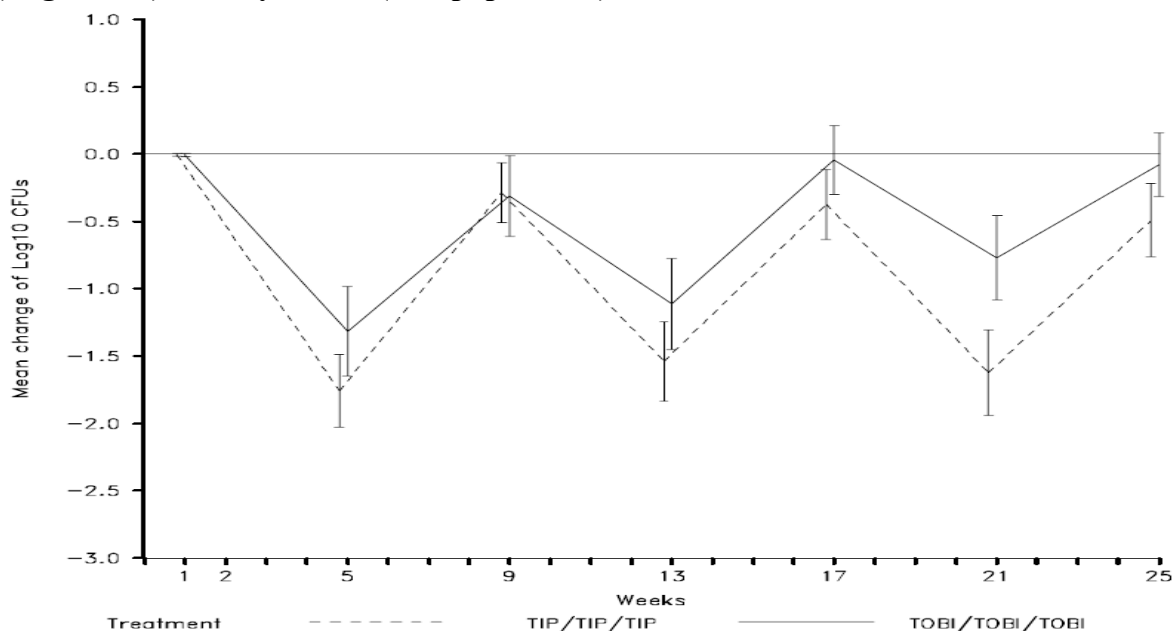
Overall density is used, and it is defined as the sum of bio-types (mucoid, dry and small colony variant). The log₁₀ is taken on the sum.

Termination visit: last available post-baseline measurement.

Source: Table 14.2-2.1, NDA submission

FIGURE 12

Between treatment comparison of change in *P. aeruginosa* sputum concentration (Log₁₀ CFU) – Study C2302 (ITT population)



Note: the vertical bar is 95% confidence interval. Overall density is used, and it is defined as the sum of biotypes (mucoid, dry and small colony variant).

Source: Figure 4-7, Clinical Pharmacology Summary, NDA submission

The confidence intervals around the mean change overlap in all cycles. Nonetheless, among all colony types combined, the test (TIP) arm reduced the mean number of *P. aeruginosa* somewhat more than the comparator (TOBI®) arm.

Changes in *P. aeruginosa* MIC During Therapy

Study C2301

The MIC summary results are shown as the maximum value of all colony types in Study C2301 when more than one colony type was present in a given patient at a given visit in TABLE 28.

TABLE 28
MIC summary for study C2301, ITT Population; maximum of colony type-1, -2, -3

Tobramycin MIC (mcg/mL)								
Range	N	TIP/TIP/TIP			N	placebo/TIP/TIP		
		Range	MIC50	MIC90		Range	MIC50	MIC90
Baseline	44	≤0.25- >512	0.5	32	48	≤0.25->512	1	8
Week 5	29	≤0.25- >512	1	>512	44	≤0.25-8	0.5	2
Week 21	28	≤0.25- >512	1	>512	30	≤0.25-256	1	32
Week 25	30	≤0.25- >512	1	128	37	≤0.25->512	1	8
Termination	40	≤0.25- >512	1	32	48	≤0.25->512	1	8

Legend: light grey= two dilution step increase over baseline; dark gray =three or more dilution step increase over baseline
Source: Table 4-13, Clinical Pharmacology Summary, NDA submission

When the MICs from all colony types are pooled and assessed, baseline MICs from isolates in the TIP/TIP/TIP treatment arm were *less susceptible* than those in the placebo/TIP/TIP arm as evidenced by the MIC90 values of 32 and 8 mcg/mL, for TIP and placebo, respectively. This represents a two-dilution difference in the baseline MIC90 values for the two treatment arms. Thus, the MIC90 of the baseline organisms in the test arm are resistant by the accepted CLSI systemic breakpoints (≥ 16 mcg/mL) for tobramycin. The reason for difference in baseline MIC90, which represents a two dilution step difference, is not clear.

The MIC90 values from all *P. aeruginosa* colony types from the TIP/TIP/TIP treatment arm were identical at termination as the MIC90 values at baseline, 32 mcg/mL. However, at weeks 5 and 21, the TIP/TIP/TIP arm MIC90 had increased to >512 mcg/mL, an increase of more than four dilution steps compared to the baseline MIC90.

In the placebo/TIP/TIP arm, the MIC90 value for *P. aeruginosa* colony types was identical at termination as those at baseline, 8 mcg/mL. The maximum change in MIC was noted at week 21, with a two dilution step increase (MIC90 increase to 32 mcg/mL).

Study C2302

The same analysis for Study 2302, when more than one colony type was present in a given patient at a given visit, is shown in TABLE 29. In this study, the MIC90s of the baseline organisms in the TIP arm (64 mcg/mL) and the TOBI® arm (128 mcg/mL) are resistant by the accepted CLSI systemic breakpoints for tobramycin.

TABLE 29

MIC summary for Study C2302, ITT population; maximum of *P. aeruginosa* colony types- 1, -2, -3

Tobramycin MIC (mcg/mL)									
TIP					TOBI®				
Range	N	Range	MIC50	MIC90	N	Range	MIC50	MIC90	
Baseline	308	≤0.12->512	2	64	208	≤0.12->512	2	128	
Week 5	239	≤0.12->512	2	512	173	≤0.12->512	4	64	
Week 21	199	≤0.12->512	4	256	154	≤0.12->512	4	256	
Week 25	201	≤0.12->512	2	256	155	≤0.12->512	2	64	
Termination	298	≤0.12->512	2	512	202	≤0.12->512	2	64	

Legend: light grey= two dilution step increase over baseline; dark gray =three or more dilution step increase over baseline

Source: Table 4-18, Clinical Pharmacology Summary, NDA submission

The MIC90 values for the colony type-2 isolates in the TIP treatment arm increased such that at both the Week 5 and termination visits, the MIC90 value had increased from 64 to 512 mcg/mL, an increase of three dilution steps. At weeks 21 and 25, the tobramycin MIC90 had increased to 256 mcg/mL, an increase of two dilution steps compared to the baseline MIC90. Except for week 25, MIC90 values on the TOBI® arm show a reduction in the MIC90 relative to baseline.

The *P. aeruginosa* dry colony type appears to be the driver for the increased MICs on therapy, as demonstrated in TABLE 30.

TABLE 30

MIC summary for Study C2302, ITT Population; Colony Type -2, dry colony variant

Tobramycin MIC (mcg/mL)									
TIP					TOBI®				
Range	N	Range	MIC50	MIC90	N	Range	MIC50	MIC90	
Baseline	214	≤0.12->512	2	64	144	≤0.12->512	2	128	
Week 5	126	≤0.12->512	4	512	99	≤0.12->512	4	128	
Week 21	107	0.25->512	8	512	81	0.25->512	8	256	
Week 25	118	≤0.12->512	4	512	96	≤0.12->512	2	64	
Termination	225	≤0.12->512	4	512	166	≤0.12->512	2	128	

Legend: gray shading =three dilution step increase over baseline

Source: Table 4-16, Clinical Pharmacology Summary, NDA submission

The MIC90 values for colony type-2 isolates in the TIP treatment arm increased such that by termination, the MIC90 value had increased from 64 to 512 µg/mL, an increase of three dilution steps. This increase was noted as early as week 5 and was sustained through termination. In the TOBI® arm, except for a single step MIC 90 increase over baseline at week 21, the MIC 90 value remained at baseline. Note that the MIC90 of the baseline isolates in the TIP arm (64 µg/mL) and the TOBI® arm (128 µg/mL) are resistant by the accepted CLSI systemic breakpoints for tobramycin.

Antibacterial Resistance Development on Therapy: Resistance to Tobramycin

CLSI systemic interpretive criteria define tobramycin resistance as an MIC ≥ 16 $\mu\text{g/ml}$ for *P. aeruginosa* isolates. The MICs for *P. aeruginosa* isolates from Study C2301 were examined and stratified by colony biotype i.e. dry, mucoid, small colony and mixed colony types for each treatment arm. TABLE 31 shows the percentage of isolates from each colony type demonstrating an increase from Baseline to the Termination visit in MIC to ≥ 16 mcg/ml, considered a resistant phenotype.

TABLE 31
***P. aeruginosa* tobramycin MIC increase by colony type, Study C2301**

Biotype	% increase by treatment arm	
	TIP/TIP/TIP N=46	Placebo/TIP/TIP N=49
dry colony	7.60%	7.20%
mucoid colony	5.40%	4.3%
small colony	18.60%	0%
mixed biotypes	8.60%	0%

Source data: Table 3.2-1.6 of the applicant's NDA submission

Increases of 5% or more in tobramycin resistance while on therapy was observed among all colony types i.e. dry, mucoid, small colony and mixed for patients in the TIP/TIP/TIP treatment arm with the greatest increase occurring among the small colony biotype (18.6%). In contrast, only the dry colony type in the in the Placebo/TIP/TIP treatment arm showed an increase in tobramycin resistance while on therapy (7.2%).

A similar analysis for Study 2302 for Study C2302 was conducted (TABLE 32)

TABLE 32
Tobramycin resistance increase by *P. aeruginosa* colony type, Study C2302.

Biotype	% increase by treatment arm	
	TIP N=308	TOBI® N=209
dry colony	6.7%	- 4/3%
mucoid colony	7.3%	- 1.4%
small colony	18.4%	-6.7%
mixed biotypes	7.8%	-2.3%

Source data: Table 14.2-3.3 of the applicant's NDA submission

Increases of 5% or more in tobramycin resistance while on therapy was observed among all colony types i.e. dry, mucoid, small colony and mixed for patients in the TIP treatment arm but not the TOBI® treatment arm. The greatest increase in resistance occurred among the small colony biotype (18.4%). In contrast, *none* of the colony types in the in the TOBI® treatment arm showed an increase in tobramycin resistance while on therapy.

Antibacterial Resistance Development on Therapy: Other Antibacterial Drugs

The Applicant examined the increased resistance levels for a variety of antibacterial drugs from baseline to the termination visit for all biotype *P. aeruginosa* isolates. Changes in resistance levels during therapy were examined for the following antibacterial drugs: aztreonam, ciprofloxacin, ceftazidime, imipenem and meropenem.

In Study 2301, no increases in resistance were noted to the following antibacterial drugs: aztreonam, ciprofloxacin, imipenem and meropenem. The only exception was an increase in ceftazidime resistance (6.3%) seen in the placebo arm.

In Study 2302, an increase resistance to multiple antibacterial drugs was seen in colony types in both the TIP and TOBI® arms. In the TIP treatment arm, mucoid colony types showed 5.9%, 7.3% and 6.5% increases in ceftazidime, ciprofloxacin and meropenem resistance, respectively. In addition, there was a 9.1% increase in ciprofloxacin resistance among mixed colony types. In the TOBI® treatment arm, dry colony types showed 6.3% and 11.2% increases in aztreonam and ceftazidime resistance, respectively. An 8.9% increase in ceftazidime resistance was also seen in small colony variant colony types. The mixed colony types showed a 5.8% increase in imipenem resistance.

Treatment Emergent Organisms in the Placebo-Controlled Phase 3 Studies: Pooled Data for Studies 2301 and 2303.

The exclusion criteria for studies C2301 and C2303 did not allow enrollment of patients that had any use of inhaled anti-pseudomonal antibacterial drugs within four months prior to screening. Therefore, organisms isolated at post-baseline visits that were not present at baseline were likely representative of true treatment-emergent organisms. Similar data was not available for Study C2302 as more recent use of inhaled anti-pseudomonal antibacterial drugs was allowed.

Organisms not present at baseline that appeared at End of Dosing or End of Cycle 1 in more than one patient in one of the treatment groups in Study C2301 and C2303 pooled data are shown in TABLE 33.

TABLE 33
**Treatment-emergent organisms present in more than one patient in pooled data-
Study C2301 and C2303**

Organism	No. Isolates ^a	
	TIP ^b	Placebo ^c
Bacteria		
<i>Achromobacter xylosoxidans</i>	2	0
<i>Alcaligenes faecalis</i>	2	0
<i>Chryseobacterium indologenes</i>	0	2
<i>Haemophilus influenzae</i>	7	2
<i>Haemophilus parainfluenzae</i>	6	8
<i>Serratia marcescens</i>	1	4
<i>Staphylococcus aureus</i> (methicillin-resistant)	1	2
<i>Staphylococcus aureus</i> (methicillin-sensitive)	6	6
<i>Stenotrophomonas maltophilia</i>	4	2
β -hemolytic <i>Streptococcus</i> , Group A	2	1
β -hemolytic <i>Streptococcus</i> , Group B	2	1
β -hemolytic <i>Streptococcus</i> , Group C	2	1
β -hemolytic <i>Streptococcus</i> , Group G	2	0
<i>Streptococcus pneumoniae</i>	1	3
Yeasts and Fungi		
<i>Candida albicans</i>	2	0
<i>Aspergillus fumigatus</i>	3	4
<i>Penicillium</i> species	4	0
Filamentous mold other than <i>Penicillium</i> / <i>Aspergillus</i>	2	2

a Total number of isolates for End of Dosing and End of Cycle 1

b No. patients = 78

c No. patients = 79

Source: Table 4-37 [SCE-Appendix 1-Table 3.4-1.10], NDA submission.

When the total number of emergent organisms was compared, there were 57 isolates among 78 TIP treatment patients and 45 isolates among 79 patients in the placebo arm. While some patients had more than one emergent organism, roughly more than 50% of patients had emergent organisms. The discrepancy in the number of emergent organisms represents 27% more emergent isolates from patients in the TIP treatment arm than in the placebo arm. This discrepancy may partly explained by the increased number of *H. influenzae* isolates in the TIP treatment arm versus the placebo arm, seven versus two isolates, respectively and the number of *Penicillium* spp. isolates in the TIP treatment arm versus the placebo arm, four versus zero isolates, respectively. *Stenotrophomonas maltophilia* isolates were more common in the TIP arms (4) versus the placebo arms (2). Two patients in the TIP arm developed infections with *Candida albicans*; no patients in the placebo arms developed infections with this organism. Total numbers for all organisms were small and this limits interpretation.

Summary of FDA Microbiology Review

The decrease from baseline in *P. aeruginosa* sputum concentration for TIP was superior to placebo and similar to TOBI®. The primary concern regarding the data in this submission is the occurrence of the reduced susceptibility of *Pseudomonas aeruginosa* to tobramycin while on TIP therapy compared to TOBI® and the consequences this may have on the

treatment outcome for the patient. In addition, there is the potential that the less susceptible *P. aeruginosa* may be transmitted to others in the immediate environment of the cystic fibrosis patient. There was increased emergence of other pathogens during TIP therapy in placebo controlled trials. However, a small number of emergent organisms isolated limits interpretation.

Compliance and Device Useability

Compliance

Compliance was assessed in the two placebo controlled studies (C2301 and C2303) and in the active controlled study C2302. Compliance was based on subject dosing logs, verified by a count of used and unused capsules (TIP) or ampules (TOBI). Compliance rate was expressed as a percentage of doses taken/doses planned or capsules or ampules used/capsules or ampules provided. The assessment based on capsules or ampules used may differ slightly over the measurement of doses taken, as more capsules were provided than needed for 28 days. In the placebo controlled studies assessment, of compliance is limited to a single 28 day cycle. The information from the active controlled study (C2302) is felt to best reflect anticipated compliance for the indication sought.

Studies C2301 and 2303

Compliance for Cycle 1 in Study C2301 favored TIP over placebo; mean compliance was 91% for TIP and 89% for placebo; low compliance (<80% compliance) was reported for 13% (6/46) of TIP subjects compared to 16% (8/49) of placebo subjects. Compliance in Study C2303 was similar between TIP and placebo. In study C2303, the TIP arm had a mean compliance of 95.5% and the placebo arm had a mean compliance of 97.2%. Interpretation of between-arm comparisons is limited as the placebo was also an inhaled powder (without tobramycin) in cycle 1.

Study C2302

TABLE 34 shows the proportion of subjects with compliance <80% by cycle using a denominator based on the numbers of subjects available at the beginning of that cycle to calculate percentages.

TABLE 34
Compliance < 80% by Cycle and Treatment Arm

	Low Compliance Per Treatment Cycle (< 80% Compliance)		
	Cycle 1	Cycle 2	Cycle 3
TIP	12% (36/308)	13% (35/264)	16% (38/234)
TOBI®	7% (14/209)	9% (17/181)	8% (14/172)

- cycle compliance = 100 x (number of doses taken in on cycle period/56)
- Numerator equals number of subjects with <80% compliance in each cycle; denominator equals number of subjects who started each cycle

Source: Reviewer Table

Given that one of the presumed advantages of the TIP drug product is ease of use, it is of note that the point estimate for the proportion with compliance <80% was actually slightly higher in the TIP arm relative to TOBI for every cycle, with a trend to increasing non-compliance from Cycle 1 to Cycle 3.

Device Usability and Comprehension

Human factors studies were conducted by the applicant in the US and EU to evaluate the ability of different subgroups to properly use the combination of drug and device. The study objective was to demonstrate successful performance of all essential and critical tasks associated with complete drug delivery per dose by representative users (one dose being equivalent to 4 capsules of study drug). Also, the study attempted to obtain subjective measures using rating scales/questionnaires.

Study design

Four distinct user groups with asthma or CF were identified and recruited for the study:

- Younger children (age 6-8), 16 participants
- Older children (age 9-12), 15 participants
- Teenagers (age 13-17), 15 participants
- Adults (age 18+), 16 participants

Pediatric users were accompanied by their caregivers with the exception of two teenagers. Caregivers were instructed to intervene only if the caregiver deemed it necessary, and not to prepare the dose for the children participating. Participants either had a clinical diagnosis of cystic fibrosis (12 participants) or of asthma (50 participants).

The study was divided into 3 distinct phases

- Phase 1: Interviews were conducted with health care provider to determine level of training required for use of device
- Phase 2: A pilot study was conducted to rehearse the study protocol
- Phase 3: A main usability study was conducted where patients and caregivers were required to:

- i. Participate in an initial interview and training session, which was followed by an observed assessment of first inhaler use; patients were also provided access to the Instructions For Use
- ii. Participate in a five day at-home use where morning and evening doses were simulated using commercial weekly patient packs with empty inhalation capsules
- iii. Participate in the final interview with a final observed assessment of use followed by participant debriefing

The design of the main usability study allowed for training decay given the one week interim period during Phase 3 and because training was done by prescribing physicians, study participants received training intended to model real world health care settings.

Study Results: Initial Training and Use

Sixty-two subjects participated in the initial training and first use assessment. 85% followed proper dosing procedures as outlined by the applicant. This involved removing capsules from blister packs, piercing capsules with the inhaler, and inhaling from 4 capsules as required for a full dose. However, other critical steps were not formally assessed including observing the subject inhale twice per capsule. Moreover, because the capsules were empty, subjects could not realistically be observed checking whether any powder remained in a capsule after inhalation during an actual use scenario.

Nine subjects (15%) did not complete successful dosing on the first attempt. Errors that occurred with particularly high frequency included participants not exhaling fully prior to inhalation (35 participants), not correctly orienting the device while piercing capsules (20 participants), not removing and checking that a capsule was pierced (20 participants), not inhaling twice from each capsule (17 participants), not cleaning the mouthpiece properly (13 participants), and depressing the button for piercing incorrectly (8 participants). Clearly, certain errors are more critical and could have more detrimental implications than others. However, it is notable that proper use of the device was not as readily adopted as would be expected with a drug device combination whose primary attraction is ease of use.

Study Results: Post One Week Assessment

There was a significant reduction from baseline in the number of participants who returned for the one week assessment. Only 34 subjects (55%) subjects returned for this study visit. Whether the subjects who dropped out represented the majority of subjects committing use errors in the initial assessment is unclear and is currently being investigated. However, despite this reduction in sample size, particular use errors still occurred with high frequency. This included not exhaling fully prior to inhalation (22 participants), not removing a capsule and checking that it was pierced (17 participants), not correctly orienting the device for piercing of capsule (15 participants), and not cleaning the mouthpiece (10 participants). Because of the small sample size, errors that would have been observed in a larger sample may not have been discovered in this study. TABLE 35 highlights errors which appeared to worsen over time from initial assessment to post one week assessment.

TABLE 35
Use Errors Increasing in Incidence From Initial Assessment to Post One Week Assessment

Errors During Use of TIP	Failure Rate Initial Assessment	Failure Rate One Week Assessment
Exhaling fully prior to inhalation	36%	54%
Misorientation during piercing	21%	32%
Checking that capsule was pierced	17%	34%
Cleaning mouthpiece	21%	26%

Other errors only mildly improved from initial assessment to the one week assessment. Importantly, subjects were not required to use the Instructions For Use (IFU) at the initial training and how the IFU was used was not formally observed. Assessing participants' understanding of whether a capsule was empty or not was captured in a separate substudy during the initial training. In this study, subjects were given capsules with different powder fills and had to decide whether to re-inhale or not. 11% of subjects decided not to re-inhale despite a capsule being at least 1/3 full.

Study Limitations and Assessment

The main usability study had several limitations. These included the use of empty capsules and the focus on completion of only some of the critical tasks of proper dosing but not others (such as inhaling twice from each capsule to deliver a full dose). Ideally, all critical steps should be performed properly and failure at any critical step during product use should be considered an overall failure of use for that subject. There was also no untrained user group. This is critical given that some adult patients may be considered to have adequate training due to use of prior inhalers and some caregivers may help to administer drug without proper training. Importantly, the number of dropouts in the study limited assessment of training decay. Lastly, there was no proper validation of the IFU. This limits understanding whether patients will be able to use the product safely and effectively if they follow the IFU. It was noted in this study that no subject read the IFU thoroughly.

Numerous errors in use were observed and important aspects of proper use were not thoroughly studied. Multiple steps are present in which an error could result in under dosing (such as not checking to see if a capsule was empty or not).

Draft Discussion Points for the Advisory Committee

1. Has the applicant demonstrated adequate evidence of efficacy to support the use of tobramycin inhalation powder (TIP) in the management of cystic fibrosis patients infected with *Pseudomonas aeruginosa*? If not, what additional data are needed?
2. Has the applicant demonstrated adequate evidence of safety to support the use of TIP in the management of cystic fibrosis patients infected with *Pseudomonas aeruginosa*? If not, what additional data are needed?
3. Please discuss the implications of the changes in mean inhibitory concentrations (MICs) seen after treatment with TIP compared to tobramycin solution for inhalation.
4. Should the application be approved, please discuss the role of TIP in the management of CF.